EXHIBIT 1

InCompliance Solutions

October 31, 2022

Adam M. Slater
Mazie Slater Katz & Freeman
103 Eisenhower Parkway
Roseland, New Jersey 07068

Dear Mr. Slater:

At your request I have reviewed materials including regulatory documents, guidances, and standards, corporate documents including emails, reports, SMP's and similar internal protocols, scientific literature, and deposition testimony, as set forth in this report and the referenced exhibits, and those documents and sources of information listed in the List of Materials reviewed attached as Exhibit B. I have applied my background, training, knowledge, and experience. I have reached opinions with regard to the manufacturing and sale of valsartan API by ZHP that resulted in nitrosamine impurities NDMA and NDEA in the valsartan API manufactured with the TEA with sodium nitrite quenching and zinc chloride processes, and the manufacture by ZHP of valsartan finished dose incorporating that API. The contaminated valsartan API containing those impurities was also sold to and incorporated into finished dose form by finished dose manufacturers Teva and Torrent, who purchased the valsartan API from ZHP and incorporated the valsartan API into their finished dose as well. There were multiple medications sold containing the contaminated API, including formulations with Hydrochlorothiazide, and these drugs are collectively referred to herein as "valsartan" or "valsartan containing drugs."

As set forth in detail herein, it is my opinion that ZHP's development and use of its TEA with sodium nitrite quenching and zinc chloride manufacturing processes for valsartan, violated CGMPs (e.g., 21 CFR §210(a); 21 CFR §211(b); ICH Q7 (Q7)). These violations included inadequate risk assessments and testing during development of the processes, inadequate risk assessment and testing in connection with the manufacture of valsartan with those processes, inadequate risk assessment and testing of manufactured batches as required in ICH Q9 (Q9), and ICH Q10 (Q10) once the drugs containing that API began to be marketed, failure to adequately assess and respond to customer complaints and evaluate unknown peaks on chromatography testing, and manufacture of valsartan with the zinc chloride process and TEA with sodium nitrite quenching process even after ZHP apparently had knowledge as of July 27, 2017 or earlier of the NDMA impurities and that the root cause of nitrosamine contamination in sartans was the quenching with sodium nitrite.

In addition, Huaihai US, Inc. as the US agent of ZHP, and Prinston Pharmaceuticals in its role as purchaser of the ZHP finished dose, which it marketed via its subsidiary Solco, who was

ZHP distributor in the United States, violated the FD&C Act and 21 U.S.C. by introducing adulterated product into U.S. Interstate Commerce. This was a violation of the Food, Drug and Cosmetic Act, sec. 301(a); and 21 U.S.C. 331(a) which states "The following acts and the causing thereof are prohibited: The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded".

As a result, the valsartan API manufactured with the TEA with sodium nitrite quenching and zinc chloride manufacturing processes and finished dose incorporating that API, failed to match the approved formulation of valsartan, including in the ANDAs and compendium. This API and finished dose was adulterated by definition, since they contained unapproved genotoxic impurities NDMA and NDEA, and was manufactured in violation of CGMPs. In this context, in a letter dated September 21, 2018, FDA notified ZHP of their unacceptable state of CGMP compliance based on an inspection performed July 23, 2018 through August 3, 2018 of their Linhai, Zhejiang Province 317016 facility, where numerous observations were cited by FDA for various deficiencies and inadequacies related to risk assessment, validation, and risk management, including justification and classification for the modified zinc chloride manufacturing process for valsartan and its active pharmaceutical ingredient (API). Additionally, ZHP was issued a Warning Letter by the FDA on November 29, 2018 summarizing significant deviations from CGMPs for the API, including but not limited to the inadequate risk assessment for the zinc chloride process, resulting in the determination that this was an adulterated product within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B). These actions focused on the zinc chloride process as that was the process as to which disclosure was first made, however the same analysis would apply to the TEA with sodium nitrite quenching process.

Background and Qualifications

My background is set forth in my curriculum vitae, attached hereto as Exhibit A, and is summarized here. I spent over 30 years in the FDA-regulated pharmaceutical and medical device industries and several years working at the U.S. FDA as a Consumer Safety Officer/Investigator. For the last 10 years, I have been a Professor, teaching graduate-level courses in Regulatory, Clinical Research and Quality Assurance/Control. Additionally, for the last 12 years I have been a consultant in the pharmaceutical and medical device industries and co-authored and co-edited a textbook titled *"An Overview of FDA Regulated Products; From Drugs and Cosmetics to Food and Tobacco."*

General Overview of CGMPs and Methodology

The manufacture of generic valsartan API by ZHP was governed by current good manufacturing practices ("CGMPs"). The applicable CGMPs are derived from regulations, industry-recognized international performance standards, regulatory guidance documents, and internal Standard Operating Procedures (SOPs)/Standard Management Procedures (SMPs). These standards are applied to facilitate and regulate product and process development, test method development, and validation and risk management during the research and

development (R&D), pre-clinical and clinical phases, and commercialization of a drug product. Companies must design and implement a robust and compliant Quality Management System to control the various systems required to manage pre- and post-commercialized product. In other words, it is not sufficient to only adopt internal procedures to ensure compliance with CGMPs; those procedures must also be applied in a robust manner throughout the lifecycle of the drug to ensure appropriate identity, quality, purity, safety, strength, and stability of the drug product. It was the duty of the quality function/department at ZHP, and the company's high level management overseeing the quality function, to apply CGMPs as required and to ensure the drug products they sold were the approved form of those drug products, with the approved identity, quality, purity, safety, strength, and stability of the drug product. As discussed herein, this duty was not met.

The methodology I applied here is the methodology I applied as an FDA investigator responsible to evaluate CGMP compliance by manufacturers, and in my interactions with other personnel at the FDA, and that I continue to apply as a consultant to manufacturers with regard to CGMP compliance, and which I teach. This methodology includes evaluation of the relevant documents and statements from those involved and with knowledge of the relevant activities, application of the applicable federal regulations, international standards including those from ICH, regulatory guidances, and assessment of whether adequate internal procedures have been adopted and also applied and implemented in the required robust manner. This is the accepted methodology applicable in the pharmaceutical industry. All of the opinions set forth herein are stated to a reasonable degree of regulatory certainty.

I have considered numerous sources of CGMP authority, which are discussed in this report, and referenced in the testimony and documents listed on my list of materials reviewed, including but not limited to:

21 CFR Part 210; Current Good Manufacturing Practices in Manufacturing, Processing, Packing or Holding of Drugs: General

21 CFR Part 211; Current Good Manufacturing Practices for Finished Pharmaceuticals

21 CFR 211.165(e) which states "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented."

21 CFR 211.80 states that "[T]here shall be written procedures describing in sufficient detail the . . . testing . . . of [finished drug product] components…."

21 CFR 211.84(d)(2) states that "[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals."

FDA Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)

FDA Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

FDA Guidance for Industry – Process Validation: General Principles and Practices (2011)

FDA Guidance for Industry – Control of Nitrosamine Impurities in Human Drugs (2021)

EMA guidelines titled "Guideline on the Limits of Genotoxic Impurities" in effect from January 1, 2007 to January 31, 2018.

ICH Q3A Impurities in New Drug Substances

ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients

ICH Q8 titled: Pharmaceutical Development

ICH Q9 titled: Quality Risk Management

ICH Q10 titled: Pharmaceutical Quality System

ICH guideline titled, "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – M7," dated February 6, 2013

Internal SOP: Guideline for Genotoxic Impurity Evaluation (No. API-R&D-002) (bates ZHP01447235-242)

SMP-017 Deviation Investigation Management System

SMP-018 Change Control System

SMP-023 Quality Risk Management

The laws of the United States are organized by subject into the United States Code. The United States Code contains the currently enacted statutory language. FDA Regulations are located in Title 21 of the Code of Federal Regulations. The Federal Food, Drug, and Cosmetic Act and subsequent amending statutes are codified into Title 21 Chapter 9 of the United States Code. Subchapter V of the Federal Food, Drug and Cosmetic Act (FD&C Act) specifically addresses drugs and devices. Title 21, Chapter 9, Subchapter V, Part A, Sections 351 and 352 specifically address adulterated and misbranded drugs respectively. Title 21, Chapter 1, Subchapter C, titled Drugs: General is further subdivided into 19 parts.

In 21 CFR §210-Current Good Manufacturing Practices in Manufacturing, Processing, Packing, or Holding of Drugs; General, Section 210.1(a) states "The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess." 21 CFR §210(b) continues, "The failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action."

To issue FDA guidance, the FDA follows the procedures required by its "Good Guidance Practice" regulation. FDA guidance describes the agency's current thinking on a regulatory issue. The Good Guidance Practice regulation, 21 CFR §10.115(b), defines "guidance document" as "documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue." 21 CFR §10.115(b)(2) continues "Guidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies. Guidance documents do not establish legally enforceable rights or responsibilities, however in practice the Guidance is adopted by manufacturers and considered to be binding.. 21 CFR §10.115(d)(2) states "You may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with you to ensure that it complies with the relevant statutes and regulations. 21 CFR §10.115(d)(3) continues "Although guidance documents do not legally bind the FDA, they represent the agency's current thinking."

In addition to recognizing and enforcing the Code of Federal Regulations and Guidance Documents, FDA recognizes the need to harmonize and align technical requirements for development of pharmaceutical products as a component of CGMPs. In 1990, FDA was a founding member, along with Europe and Japan, of the International Council for Harmonization (ICH), an international nonprofit association composed of regulatory authorities and pharmaceutical industry to harmonize scientific and technical aspects of drug development and marketing and harmonize requirements to ensure safe, effective and high-quality drugs are developed and registered. This is accomplished through the development of internationally harmonized Guidelines in the areas of Safety, Efficacy and Quality. FDA encourages implementation of ICH Guidelines by pharmaceutical regulatory authorities globally. These are a set of guidances to ensure safe, effective and high-quality medicines are developed, registered, and maintained. They are developed through input by technical experts from regulatory and industry. ICH standards addressing CGMP include for example those found in ICH Q7, which closely mimics 21 CFR Part 211. Specific ICH Guidelines, recognized by FDA as Q7, Q8, Q9 and Q10 are and cited by FDA in various guidance documents and used extensively in pharmaceutical

API development (ICH Q7), pharmaceutical development (ICH Q8), Quality Risk Management (ICH Q9) and Pharmaceutical Quality System (ICH Q10). (*See* Food & Drug Admnistration, *International Regulatory Harmonization* (Mar. 26, 2020), https://www.fda.gov/drugs/cder-international-program/international-regulatory-harmonization. The ICH Q9 guideline provides details and tools for risk management in pharmaceutical quality. The areas of pharmaceutical quality include development, manufacturing, distribution and inspection throughout the lifecycle of the API and finished drug product. Q9 was first approved by the Steering Committee in November 2005.

As discussed herein, ZHP's failure to implement and adequately apply its own internal SMPs to fulfill its CGMP obligations is a significant aspect of ZHP's CGMP violations. All changes or modifications to the API or finished drug processes and/or testing must be evaluated to ensure there is no compromise to the FDA approved products' identity, safety, quality, purity, or efficacy, and this did not happen here. All changes must be reviewed and approved by responsible personnel who have the appropriate education, background and experience to perform these assessments in a scientifically rigorous manner, and to fulfill their duty to make adequate, informed quality assurance and quality management decisions based on that scientific analysis, and this did not occur here, in large part due to the failure by ZHP to apply scientific knowledge and literature in a rigorous manner.

The application of CGMPs is an ongoing obligation, and was applicable to every stage of the lifecycle of ZHP's Valsartan on a daily basis from the first day to the last day of the lifecycle, including development of the manufacturing process, the actual manufacturing process once utilized to manufacture product for sale, testing, product release, ongoing quality assurance and management, responses to signs of potential quality issues including ongoing risk assessment and testing, and responses to complaints from commercial and retail customers and regulators indicating potential quality issues. The risk assessment and risk management functions must be applied and satisfied at all times on an ongoing daily basis by the manufacturer's quality organization, which in the case of ZHP, failed to discharge its CGMP duty to ensure the quality, purity, and identify of the valsartan drug product at issue. 21 CFR §210.1(a) states "The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

Risk management is a broad and systematic process for assessment, control, communication and review of risks to the quality of a drug throughout its lifecycle. Decision points are set throughout the development process, and includes changes or modifications made after FDA approval and commercialization. Risks are required to be defined, identified, assessed, analyzed, evaluated and controlled to reduce risk to an acceptable level. These risks are communicated to decision makers and documented. The risk management process will continue for all events that might impact product quality for FDA approved drugs or the original risk management decision, for the lifecycle of the drug.

The manufacture of generic finished dose by ZHP was also required to be in conformance with CGMPs, and the above referenced sources of authority. Regulations applicable to finished dose manufacturing can be found in 21 CFR Part 210; Current Good Manufacturing Practices in Manufacturing, Processing, Packing or Holding of Drugs: General, which discusses the status and applicability of CGMPs and in 21 CFR Part 211; Current Good Manufacturing Practices for Finished Pharmaceuticals, containing regulations for preparation of drug products for humans and animals. This addresses a wide range of activities, including drug quality, safety and purity, testing, organization and personnel, buildings and facilities, equipment, control of components and drug product containers and closures, product and process controls, packaging and labeling control, holding and distribution, laboratory controls, records and reports, and returned and salvaged drug products.

Finally, Prinston and Solco, as the marketer/distributor of the finished dose was required to ensure that the manufacture of the finished dose was in conformance with CGMPs. Hai Wang of Huahai US, Inc., Prinston, and Solco described Prinston and Solco: "Prinston is the corporate of the pharmaceutical organization, it's the corporate body…Prinston pretty much does everything except the manufacture and except the marketing and sales as a pharmaceutical company. And the marketing and sales is through Solco…Solco is the marketing arm for Prinston Pharmaceutical…" (Hai Wang 3/10/21 Dep. Tr. 218:23-220:9).

General Overview of ZHP's Manufacture and Sale of Valsartan

Valsartan is a generic drug known as an angiotensin receptor blocker ("ARB"), used for the treatment of high blood pressure, and other cardiovascular conditions. The brand name drug, which is the reference listed drug ("RLD") is Diovan, and another version of the brand name drug was Exforge, which was a combination of valsartan and amlodipine, which is a calcium channel blocker. The brand drugs were sold by Novartis pursuant to an NDA in the United States. The approved forms of Diovan and Exforge did not include NDMA or NDEA impurities in any regulatory or compendial document describing the approved form of those drugs. (ZHP01303141; ZHP02614594; https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html; Novartis, *Novartis Pharmaceuticals Corporation (Novartis) Statement on Recall Outside the United States of Sandoz Generic Valsartan and Sandoz Valsartan and Hydrochlorothiazide Film-Coated Tablets* (July 16, 2018) (stating: "The valsartan API (active pharmaceutical ingredient) in these products does not come from the same source as those products affected outside the United States. Patients in the United States currently taking Sandoz valsartan tablets, Sandoz valsartan and hydrochlorothiazide tablets, Sandoz amlodipine and valsartan tablets, Sandoz amlodipine, valsartan, hydrochlorothiazide tablets, Diovan®, Diovan HCT®, Exforge®, Exforge HCT® or Entresto® should continue to take their medication as directed by a physician."), https://www.novartis.com/us-en/news/novartis-pharmaceuticals-corporation-novartis-statement-recall-outside-united-states-sandoz-generic-valsartan-and-sandoz-valsartan-and-hydrochlorothiazide-film-coated-tablets).

ZHP manufactured valsartan using a series of manufacturing processes. The NDMA and NDEA impurities at issue were the result of changes in the manufacturing process in the absence of adequate risk assessment (along with related CGMP violations). One of ZHP's Deviation Investigation Reports prepared by ZHP and ultimately submitted to the FDA provides "Historical background information of Valsartan manufacturing process," and indicates that "There are three synthetic routes of Valsartan in Huahai Chuannan Site, including Tin process, TEA process and $ZnCl_2$ process." ZHP Deviation Investigation Report dated November 5, 2018 (DC-18003, PRINSTON0075797), beginning at 56 of 236 ("TEA DIR"). According to Table 4-3, the "Summary of Valsartan production history" at 62-63 of 236:

- The Tin process was utilized in Workshop 4 from October 2006 to March 2011, and in Workshop 2 from September 2010 to May 2014.

- The TEA process without sodium nitrite quenching was utilized in Workshop 4 from June 2008 to July 2011, and in Workshop 2 from December 2010 to May 2011.

- The TEA process with sodium nitrite quenching was utilized in Workshop 2 from May 2011 to May 2014, in Workshop W02 from May 2012 to March 2013, and in Workshop 4 from July 2011 to July 2015.

- The zinc chloride process was utilized in Workshop 2 beginning in November 2011 (no end date provided), and in Workshop W02 beginning in April 2012 (no end date provided).

These dates correspond to the dates provided in Table 4-1 at 57-58 of 236, providing the dates of process validation and registration. Of note, following table 4-3, ZHP states at 63 of 236, "it indicates that different manufacturing processes for Valsartan may coexist in Workshop 2, Workshop 4 and Workshop W02." This is an indication of the conditions that created the potential for cross-contamination between the TEA with sodium nitrite quenching and zinc chloride processes due to inadequate cleaning of shared production lines, and inadequate testing of the drug products due to the failure to test for the foresseable presence of NDMA and NDEA. These were ongoing CGMP violations throughout the period of time that the contaminated drug products were manufactured and sold.

A summary of the relevant differences between the processes provides a clear demonstration of the root cause of the NDMA and NDEA. In summary, ZHP initially manufactured its valsartan API with what was referred to by ZHP as the Valsartan Tin process. This process utilized [redacted] as a catalyst for [redacted], the solvent used in the crude step. Of note: "no dimethylamine and its derivative reagents were used. No nitrite was used for quenching after reaction. 2. Triethylamine hydrochloride is not used, and sodium nitrite is not used to quench. No NDMA or NDEA impurities will be formed." The conclusion was that this process, which was the process utilized by the brand/RLD manufacturer Novartis, could not create NDMA or NDEA. TEA DIR at 60-61, 68 of 236.

Thereafter, as set forth at pages 57-62 in the TEA DIR, in 2011 ZHP developed a new process which it termed TEA without sodium nitrite quenching, then the TEA process with sodium nitrite quenching, and yet another new process, the zinc chloride process which also included sodium nitrite quenching. The NDMA and NDEA impurities at issue were formed as a result of chemical reactions occurring during the TEA with sodium nitrite quenching and zinc chloride processes. As stated in the TEA DIR, "NDMA is generated by nitrosation reaction of the simultaneously presented dimethylformamide (containing degradation product/impurity dimethylamine) and nitrous acid; NDEA is similar to NDMA in structure, and the formation mechanism is similar too, i.e., Nitrosation of diethylamine. (TEA DIR at 145 of 236). These chemical reactions were not adequately evaluated by ZHP at any point in the products' lifecycle.

As discussed herein, ZHP also indicated the likely occurrence of cross-contamination due to inadequate cleaning of shared production lines, and potentially also due to deficiencies in solvent recovery. The inadequate risk assessments led to further CGMP violations and the failure by ZHP to test for or identify the NDMA and NDEA during process validation and then once the valsartan was commercially manufactured and sold both directly via ZHP through its vertically integrated supply chain of Huahai, US, Prinston, and Solco, and via sales of the API to finished dose manufacturers Teva and Torrent.

The NDMA and NDEA impurities in ZHP's valsartan API and finished dose was first disclosed to ZHP's customers, and the FDA and other regulatory authorities in June, 2018. According to the documents provided, this occurred after ZHP's API customer Novartis in Europe was sold API manufactured with the $ZnCl_2$ process. Novartis tested the API and noted unexpected/unknown peaks on gas chromatography. A third-party laboratory retained by Novartis, Solvias, identified NDMA using gas chromatograpy and mass spectrometry. ZHP notified Prinston on June 6, 2018 that it believed the impurity causing unexpected/unknown peaks on gas chromatography was NDMA. Prinston notified the FDA as ZHP's agent, on June 18, 2018. (ZHP00400220; ZHP00400281; ZHP00400236; PRINSTON0000022).

I have been provided the Stipulation of Zhejiang Huahai Pharmaceutical Co., Ltd., dated May 13, 2022, which I have been advised constitutes established facts that can be relied on. The Stipulation states:

STIPULATION OF ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Pursuant to Special Master Report and Order No. 56, in exchange for Plaintiffs' agreement not to further examine a witness at deposition regarding the statements identified herein, Defendant Zhejiang Huahai Pharmaceutical Co., Ltd. ("ZHP") hereby stipulates as follows:

1. ZHP states that there are no health benefits associated with the presence of NDMA or NDEA in valsartan.

2. ZHP states that the publication *Purification of Laboratory Chemicals* (4th ed.) by W.L.F. Armarego and D.D. Perrin, which was first published in 1996 and documented scientific knowledge at that time, states on page 192 that DMF "[d]ecomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide."

3. ZHP states that it was required to perform a risk assessment in connection with the process change to the zinc chloride process. ZHP further states the following:

    a. ZHP states that the scientific research relied on to use DMF as part of the zinc chloride process did not include scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process.

    b. The risk assessment of DMF did not specifically evaluate whether DMF was degrading to yield dimethylamine as part of the zinc chloride process.

    c. Therefore, there is no document from Shanghai SynCores or ZHP that documents that potential degradation of DMF as part of the zinc chloride process was evaluated as part of the risk assessment for the zinc chloride process.

    d. ZHP states that it did not perform a risk assessment on the potential degradation of DMF because it did not realize that DMF would degrade in the way it ultimately degraded in the zinc chloride manufacturing process of valsartan. ZHP is not saying that it was not possible to know that DMF could degrade.

    e. ZHP never identified the nitrosamine impurities in connection with its 2011 Risk Assessment and therefore did not evaluate the nitrosamine impurities as part of any steps of the risk assessment process.

4. With regard to the Change Request Form identified as Exhibit 195 to the March 28/29, 2021 deposition of Peng Dong (copy of Exhibit attached hereto as Exhibit 1), ZHP states the following:

    a. The "Explanation Section" in Section 2 of the Change Request form on the page bearing Bates number ZHP01843067 provides a summary of the explanation for why the process change from the triethylamine hydrochloride process to the zinc chloride process was undertaken.

    b. One of the reasons for the quality review described in Section 3 of the

Change Request Form on the page bearing Bates number ZHP01843069 was to identify impurities due to the new process.

c. Section 3 of the Change Request Form on the page bearing Bates number ZHP01843070 provided that if this change was against CGMP code, it was supposed to be rejected.

Based on my review of the materials provided, ZHP stipulated to facts establishing deficient risk assessments and quality review during the development of the zinc chloride process, in connection with the manufacturing change, and thereafter. These were ongoing violations throughout the lifecycle of the process. As stated by Stephen Hecht, Ph.D. on page 19 of his report dated July 6, 2021:

"From the perspective of organic chemistry, as discussed herein, and as recognized in ZHP's own root cause investigation (See ZHP Deviation Investigation Reports, ZHP00007221, PRINSTON0073443, PRINSTON075797, PRINSTON0076100), a scientifically reasonable assessment of the Process Change would have identified the risk of formation of nitrosamine impurities, would have presumably led to testing for nitrosamines, and would have confirmed the formation was occurring. In addition, from an organic chemistry perspective this Change met the definition of a "Critical Change – A change which has direct or potential impact on product identity, strength, quality, purity and regulation, or have impact on validated Procedure, method, qualification or equipment." This was a critical change because the process change had the foreseeable capacity to create, and resulted in, dangerous NDMA contamination. This analysis applies as well to the change from the TIN process/TEA process to the TEA process with sodium nitrite quenching, which resulted in the formation of NDEA and NDMA. In light of the known potential results of the chemical processes, identification of the clearly foreseeable NDMA and NDEA impurity contamination could have been easily accomplished."

ZHP acknowledged that the terms of its own internal change control procedure required the change to be "rejected" since the "change was against CGMP code." The requirement to reject the change to the zinc chloride process was ongoing throughout the lifecycle of the drug product. At any point that NDMA or NDEA was detected this would have required a halt to the manufacturing and sale of product with the offending process, requiring an immediate risk assessment and root cause analysis, and filing of a Field Report with the FDA. (PRINSTON00000001-46).

The Site Master File for APIs, for the Chuannan Site, version SMF-API-14 dated October 10, 2011 was approved by Jucai Ge. (HUAHAI-US00010173) describes the facilities, organization, quality activities, including C.2.6 the requirements per SMP-20, providing that "products should be reviewed annually by responsible departments," requiring extensive analysis, "in order to check whether the process remains reliable, the current specification for raw materials and final products remains suitable. The annual review helps to observe any unexpected trend and decide if product or process optimization is required." In addition, "Quality risk management covers the whole life cycle of API and drug substance, including R&D, production, distribution,

inspection, submission and review, etc. and also including the raw materials, solvents, packaging materials and labels."

As stated in Section 3(e) of the Stipulation, the nitrosamine impurities were not evaluated "as part of any steps of the risk assessment process." The same was true on an ongoing basis before and after ZHP began to market the valsartan containing NDMA. This constituted ongoing CGMP violations for the lifecycle of the manufacturing process, since the risk assessment was required to be conducted on an ongoing basis with regard to the manufacture and sale of each batch throughout the lifecycle of the drug. In other words, the CGMP violations did not end following the early development and validation stages prior to marketing, or at the time of submission of the DMF or the ANDA, but rather continued every day during the drug's lifecycle. For example, following approval of Prinston's ANDA, ZHP, Huahai, US, and Prinston failed to adequately identify the need to test any of the batches of API and finished dose product intended for sale, to rule out the presence of nitrosamines including NDMA, and failed to perform that testing, and as a result did not detect indications of or the presence of NDMA. Thus, the valsartan that was sold contained unacceptable genotoxic impurities and was materially different from the approved valsartan – which did not list NDMA or any nitrosamines as impurities, much less as acceptable or approved.

This analysis is equally applicable to the TEA process with sodium nitrite quenching, as the same violations occurred in that context also. If CGMPs had been adhered to at any point, and the NDEA and NDMA had been detected, ZHP would have been required by the terms of its own internal protocols and procedures, and regulatory guidances relied on including ICH, not to utilize that process to manufacture valsartan API or finished dose product. ZHP would also have been required to notify Prinston about the NDMA, which would have required Prinston to notify the FDA and its customers, and to cease sale of the drug product containing NDMA. ZHP would have been required to notify Teva, Torrent, and its other customers of its API as well.

Moreover, ZHP could have modified the processes to prevent the creation/presence of NDMA or NDEA in the drug product, for example by reinstating the TIN process, or by removing the product prior to sodium nitrite quenching so that the product could not be contaminated by the reactions during the quenching process. In this connection, ZHP established that the zinc chloride process could have been optimized to prevent NDMA in the product by extracting the product prior to quenching the sodium azide, "any formation of NDMA will not be carried over into the product," and that this would not require any change to the manufacturing process, "This approach can be done without any change of manufacturing process." July 1, 2018 Investigation of the Source of this Impurity (NDMA) (ZHP01495188). This is also addressed in detail in the TEA DIR at 29-35 of 236, stating in part: "After optimization, the ROS remains the same, the product in Valsartan Crude Step (Step 4) is separated before the addition of $NaNO_2$ (and the subsequent addition of HCl)…Therefore, the product in the organic phase has no chance to be contaminated by NDMA." These options would not have introduced a substantial risk of adverse effect on the identity, quality, purity, strength, or stability of the drug products, but rather would have eliminated the risks introduced with the NDMA and NDEA created with the

TEA with sodium nitrite quenching and zinc chloride process. This is addressed by Dr. Hecht in his July 6, 2021 and October 31, 2022 reports, and by Dr. Najafi in his October 31, 2022 report. ZHP could have documented these changes by filing DMF amendments, and the ANDA holders relying on the filed DMF could have included this information in an annual report or at most filed a CBE-30 with the FDA. ZHP could also have simply modified the validation specifications and testing to include appropriate testing for NDMA and NDEA. In addition, NDMA and NDEA formation due to cross-contamination introduced by shared production lines and solvent recovery equipment could have been eliminated by implementing and enforcing appropriately validated equipment cleaning and solvent recovery protocols, and testing specifications including appropriate testing for nitrosamines including NDMA and NDEA.

Dr. Hecht's July 6, 2021 report also establishes that ZHP could have identified the NDMA contamination once it performed chromatography testing and noted aberrant or unknown peaks, stating on page 20, "Analysis of the Valsartan batches manufactured by ZHP with the zinc chloride process showed the presence of an unknown peak eluting just after toluene in the GC-MS analysis." As noted by Dr. Hecht in his July 6, 2021 report on page 20, ZHP's API customer Novartis identified the NDMA based on those peaks as of June 6, 2018, whereas ZHP failed "to account for nitrosamines." As stated by Dr. Hecht on page 23 of his July 6, 2021 report: "Thereafter, when aberrant peaks demonstrated unaccounted for impurities, the nitrosamine contamination could have been easily discovered based on knowledge of the potential chemical reactions and application of GC-MS to identify potential NDMA/NDEA. This was identified by Novartis even without the full information available to ZHP." Dr. Najafi's report is to the same effect. This is an important point from a CGMP perspective, since the risk assessment duty was ongoing throughout the lifecycle of the drug product. At all times, with every batch produced, ZHP was required to apply the available scientific "knowledge of the potential chemical reactions," and then to utilize the "application of GC-MS to identify potential NDMA/NDEA." The failure to do so, both before and after approval of the ANDA's, resulted in ZHP's vertically integrated sale of valsartan API and finished dose product, and Teva and Torrent's sale of finished dose product, containing NDMA/NDEA as the approved form of valsartan, when in fact it contained NDMA/NDEA and thus was not the approved form of valsartan.

Moreover, ZHP apparently became aware of the presence of NDMA in the valsartan, and the root cause due to the quenching with sodium nitrite, as of at least July 27, 2017 per the Jinsheng Lin email discussed herein. The continued use of the zinc chloride and TEA with sodium nitrite quenching manufacturing processes thereafter, constituted further ongoing CGMP violations due to the continued use of a manufacturing process known to be causing contamination of the drug product with genotoxic impurities, with no disclosure to customers and regulatory authorities.

Finally, when ZHP, Huahai, US, Prinston, and Solco represented to their customers, the medical community, and those paying for the valsartan that they were being sold the approved valsartan, that was inaccurate since the description of what was approved in the ANDA did not include NDMA. Hai Wang of Huahai, US, Prinston, and Solco, testified that at all times it was represented that the valsartan that was sold met USP standards, "the product released and

distributed in the US at all times met appropriate standards reviewed and approved by the FDA…," that it was Orange Book AB rated "that means it's the therapeutic equivalent of the brand name product…has the same quality and purity as the brand name product," and "also is a representation that the drug was manufactured in compliance with current good manufacturing practice regulations." (Hai Wang 3/10/21 Dep. Tr. 52:2-84:19). These representations were inaccurate, since the valsartan that was sold by ZHP and its supply chain down through Solco, and that was sold to Teva and Torrent, contained NDMA/NDEA, which was never approved by the FDA, was never included in the compendial description of the drug product, and the manufacture of that drug substance did not comply with CGMP. This analysis applies to the valsartan finished dose manufactured with the zinc chloride process and the TEA with sodium nitrite quenching process.

It is my understanding that valsartan API manufactured with the zinc chloride process was sold to Teva (and its predecessors or affiliates including Watson, and Actavis, which are grouped together here under the heading Teva) and then utilized by Teva in the manufacture of Teva finished dose valsartan for sale in the United States. Teva unequivocally notified ZHP that it had sustained damages due to its use of the valsartan API that contained NDMA. In the September 13, 2018 letter from Teva to ZHP, Teva stated in part, (Teva-MDL-2875-00324735):

"By letter dated June 20", 2018, Teva received formal notification from Huahai, indicating a previously unknown impurity was identified that may have genotoxic potential with respect to Valsartan API. This notification was followed by a subsequent notification letter dated June 25, 2018, indicating that based on a preliminary investigation, the previously unknown impurity was suspected to be NDMA, and was likely to be process-related."

It is my understanding that valsartan API manufactured with the TEA process with sodium nitrite quenching was sold to Torrent and then utilized by Torrent in the manufacture of Torrent finished dose valsartan for sale in the United States. As set forth below, ZHP used the TEA with sodium nitrite quenching process through July, 2015. Torrent has unequivocally notified ZHP that it never would have purchased the valsartan API manufactured with the TEA process with sodium nitrite quenching if it had known of the NDEA and NDMA, having relied on the DMF and ZHP's representations as to genotoxic impurities, which did not disclose the NDEA or NDMA. In the February 13, 2019 letter from Makesh Agravad of Torrent to "Mr. Zenson, ye" of ZHP, Torrent stated in part, in paragraph 5 (ZHP02592303):

"As notified in Huahai in its various communications to Torrent starting from 20.06.2018, it is now clear that contrary to Huahai's declarations regarding the absence of genotoxic impurities, the API supplied by Huahai to Torrent did contain certain genotoxic impurities, namely, N-Nitroso-dimethylamine ("NDMA") and N-Nitrosodiethylamine ("NDEA") on account of the manufacturing process employed by Huahai and thus there has been a clear breach of the representations and warranties provided by Huahai to Torrent. It is also clear that these impurities were present in all batches of the API supplied by Huahai. Since NDMA and NDEA have been classified as a probable human carcinogenic, Torrent had to recall all its existing batches of

formulations containing Valsartan from the various jurisdictions, including, United States and stop any further sale."

ZHP has documented the levels of NDMA and NDEA resulting from the at-issue manufacturing processes. ZHP's September 1, 2018 Response to DMF Information Request Letter (ZHP00079913) includes Table 1, titled NDMA Test Results for Batches Manufactured Using the ZnCl Process at page 8 of 33. The table demonstrates the results of testing of 783 batches, all containing NDMA well in excess of the 0.3 ppm level the FDA adopted as an interim limit, and later adopted as a final limit for NDMA. Table 2, titled NDMA Test Results for Batches Manufactured Using the TEA Process at page 27-28 of 33 demonstrates the results of testing of 55 batches, most containing NDMA and in each instance the NDMA level exceeds 0.3 ppm. ZHP's Deviation Investigation Report, dated November 11, 2018, titled Investigation regarding unknown impurity (genotoxic impurity) of Valsartan API (TEA process), provides NDEA levels for the TEA process with sodium nitrite quenching for valsartan API. (PRINSTON0075797). Six validation batches had NDEA results of 0.03, 5.33, 12.77, 13.60, 18.83, and 13.51 ppm. (PRINSTON0075846). A separate table in that Report provides ranges and averages for the testing of 85 batches manufactured with the TEA process, documenting a range of 0.03-42.14, and average of 13.46, presumably in ppm. That table also shows NDEA levels in 111 batches manufactured with the zinc chloride process, documenting a range of 0-4.23 and average of 0.18, presumably in ppm. (PRINSTON0075858). The NDEA in zinc chloride manufactured valsartan would have been cumulative to the NDMA since there was NDMA in all zinc chloride batches.

The September 1, 2018 Response to DMF Information Request Letter responds at page 29-30 of 33 to a question regarding a batch that was confirmed to have been manufactured with the TEA process with sodium nitrite quenching. ZHP confirmed that the TEA process with sodium nitrite quenching was last used to manufacture valsartan API for the US market in July 2015. This is consistent with the manufacturing dates per the TEA DIR cited above. Of note, ZHP's testing of this batch demonstrated NDMA of 63.1 ppm (and FDA testing was approximately 50 ppm), and ZHP advised this could not be a process related impurity due to the "elucidated generation mechanism of NDMA," which was described only in the context of the zinc chloride process (use of DMF, impurity/degradant dimethylamine, reaction with nitrous acid "during the subsequent quenching step in the presence of the product"). This information was at least partially incorrect, since we know from the TEA DIR and witness testimony that the TEA with sodium nitrite quenching process created impurities in a similar manner to the zinc chloride process due to reaction of triethylamine degradants with nitrous acid during the quenching in the presence of the product (as described in the July 27, 2017 Jinsheng Lin email). Instead, ZHP stated: "Probable contamination is suspected as source of this impurity in the TEA process, such as raw material, contamination due to shared production line etc., the investigation is ongoing." This is consistent with ZHP's recognition in the TEA DIR that there was cross-contamination due to shared production lines. ZHP's lack of adherence to appropriate CGMP procedures applicable to cleaning and preventing cross-contamination when they used shared production facilities, and potentially solvent recovery operations resulted in more CGMP violations. (ICH Q7 Section VIII.E.; 21 CFR 211.67(a); 21 CFR 211.67(b); 21 CFR 211.67(b)(3); 21 CFR 211.67(b)(6) (*see, e.g.*,

SOP DB-1096-5; SOP DB-1097-5 (ZHP00373132-373145). However, consistent with ZHP's overall pattern of denial, ZHP stated, "Production in Year 2013, 2014 and 2015 is reviewed, all relevant Valsartan batches were manufactured as per GMP regulation and registered procedures." This despite admitting to likely cross-contamination which is proof of CGMP violations. Of significant note, the production records for this contaminated batch indicated full CGMP compliance, providing an example demonstrating that ZHP's internal quality records confirming CGMP compliance are not reliable.

The results for the API are applicable to the finished dose as well, as testified to by Minli Zhang and Hai Wang who confirmed this is what ZHP represented to the FDA (cited below), and this is also confirmed in Dr. Hecht's July 6, 2021 and October 31, 2022 reports, and in Dr. Najafi's report dated October 31, 2022.

Eric Gu of Shanghai Syncores/ZHP, which developed the zinc chloride process in the laboratory confirmed that if the NDMA and NDEA in the valsartan API manufactured with the zinc chloride and TEA process with sodium nitrite quenching had been known the drug products could not have been sold: "If we known that, it shouldn't be sell on the market." (Eric Gu 4/6/21 Dep. Tr. 391:12-394:7, 395:10-397:10). Hai Wang similarly testified that "if that spec has been establishes, and the product has NDMA level exceeding that 96-nanogram part, the product … [c]ould not be sold because it's not meeting spec, period." (Hai Wang 3/10/2021 Dep. Tr. 301:6-13). As testified to by John Iozzia, Director of Marketing for the API division of Huahai, US, the API sold by ZHP was not "supposed to contain dangerous unintended impurities…If it was determined that there was such an issue with the product, then it would not be a quality product." (John Iozzia 1/20/21 Dep. Tr. 21:1-22:9, 79:12-80:2). Further, Mr. Iozzia testified that there was not, "any customer you're aware of that would purchase Valsartan API if they knew that it was either contaminated or it might be contaminated and that could not be ruled out.." (John Iozzia 1/20/21 Dep. Tr.294:2-14).

ZHP's finished dose manufacturing unit was required to, but failed to comply with CGMPs as well. In the CGMP regulations for finished pharmaceuticals, 21 CFR 211.80 states that "[T]here shall be written procedures describing in sufficient detail the . . . testing . . . of [finished drug product] components…." Additionally, 21 CFR 211.84(d)(2) states that "[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and **provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.**" Therefore, if the finished drug product manufacturer accepts the test results from an API supplier's COA rather than performing the tests itself (other than for identity, which the manufacturer is required to perform), the manufacturer must validate the API supplier's reliability. **This validation procedure is established by the finished drug product manufacturer and should be consistent with the principles of CGMP and risk management.** The finished drug product manufacturer should also ensure that compendial-grade APIs comply with USP specifications, either by testing the APIs or by validating API suppliers' reliability, as described above." It is the

responsibility of the finished drug product manufacturer to ensure that the APIs they use in their products meet established standards and for compendial APIs, meet USP requirements. Since the Valsartan finished dose per the ANDA approved by FDA is manufactured using a compendial API, it must meet USP requirements, which does not include NDMA or NDEA. As referenced above, it is the responsibility of the finished dose manufacturer to perform sufficient testing of the API to ensure compliance to the compendial USP requirements. This testing must be performed on each batch of API used in the manufacture of finished dose product.

ZHP implemented internal operating procedures to address the CGMP duties of the finished dose unit. This included SMP-016.05 Management System for Formulation material supplier, which required Xunqiao to confirm qualification of all API suppliers, with regard to both the supplier and each product purchased from the supplier. (Minli Zhang 3/24/2021 Dep. Tr. 254:9–255:2). Minli Zhang could not confirm that Chuannan was requalified as a supplier prior to commercialization of the valsartan finished dose product, or that Chuannan submitted a supplier questionnaire to Xunqiao QA as part of a supplier qualification, despite these steps being required by the SMP. (Minli Zhang 3/24/2021 Dep. Tr. 263:21-264:17, 266:22–268:14).

SOP G-1005-2 Material Release Procedure addressed API obtained for use in the manufacture of finished dose. The SOP states its purpose to, "make sure material meet specifications and guarantee the product quality." Section 5.2.1 provided for API manufactured at the Chuannan site to be subjected to full testing of the first three batches after receipt of the Certificate of Analysis, pursuant to the in-house specification. Per 7.7 finished product could not be released until the testing confirmed the in-house specifications were met, and any atypical test results were closed. The SOP had no provisions related to review of manufacturing changes, but instead this activity would "fall into the change management procedure which is under the Supply Management Procedure." Minli Zhang 3/24/2021 Dep. Tr. 307:15-308:17). The SOP required Xunqiao to conduct full testing at least three times a year, however Xunqiao never conducted their own residual solvent testing of the valsartan API manufactured at Chuannan, and instead only relied on the testing conducted at Chuannan to determine whether it met specifications. (Minli Zhang 3/24/2021 Dep. Tr. 316:12–317:24). In this connection, QS-A004.05 Quality Standard for Valsartan USP provided for reduced testing of API manufactured at the Chuannan site. This standardized reduced testing due to the relationship between Chuannan and Xunqiao is not consistent with CGMPs, and the abdication of quality evaluation by the finished dose unit in favor of reliance on the API unit's quality assurance testing renders the finished dose unit responsible for the API unit's deficiencies.

Companies or product license holders using contract manufacturers to produce their APIs and finished drug products are responsible for assuring CGMP compliance for activities performed at these facilities. Quality Agreements are used to delineate their manufacturing activities and responsibilities. As described in Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry, there are a number of activities a contract manufacturer may perform for APIs and finished drug product such as formulation, chemical synthesis, packaging and labeling, analytical testing etc.. These agreements define and describe the responsibilities of parties involved in the contract manufacturing operation. The guidance

document states "Each party engaged in the manufacture of a drug is responsible for ensuring compliance with CGMP for the manufacturing activities it performs. For both owners and contract facilities that conduct manufacturing operations, CGMP, "includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products." Drugs not manufactured in compliance with CGMP are adulterated."

Just as API and finished dose manufacturers must, contract manufacturing organizations (CMOs) follow Q7, Q9, and Q10 guidelines with respect to contract manufacturing arrangements. Q7 recommends owners evaluate contract facilities to ensure that contractor sites comply with CGMP and that owners have approved written agreements with contractors that define the manufacturing responsibilities in detail, including quality measures for each party. These Quality Agreements describe how changes to processes, equipment methods and specifications will be managed. Additionally, the agreement allows for the owner to audit its contractor's facilities for CGMP compliance. Q9 also addresses quality agreements and auditing for risk management principles such as risk assessment, risk communication and risk review. These are essential tools both parties can use to make effective and efficient risk-based decisions.

As outlined in Q10, Pharmaceutical Quality System, the owner is responsible to assure processes are in place to control outsourced activities and quality of purchased material, and these activities should incorporate quality risk management and include assessment of the suitability and competence of potential contractors in selecting material, defining manufacturing responsibilities and communication processes, review of performance of the contract facility and identifying and implementing any needed improvements and monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed-upon supply chain.

The Quality Agreement between Prinston and ZHP (Hauhai) for contract manufacturing was entered into January 25, 2016, with the purpose to ensure roles and responsibilities are clearly defined with respect to CGMPs and applicable laws. (per Remonda Gergis, the initial quality agreement was entered in 2011, see below). The Quality Agreement is a detailed checklist of activities associated with pharmaceutical production, analysis, release and distribution. The checklist allows for identification of each activity to be performed and who will be responsible. The guidance document, "Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry" Section 1.d. "Product-specific considerations" states "The quality agreement also should indicate how owners will transfer knowledge, such as product and process development information, to contract facilities to ensure a drug can be manufactured in compliance with CGMP, and conversely how contract facilities should share with owners product quality information gained throughout the product life cycle. This applies to knowledge about all drugs, including drugs subject to an approved application (e.g., new drug application)….". This guidance makes clear the responsibility of both ZHP as the API, or "component" manufacturer and Prinston. ZHP was responsible for immediately notifying Prinston of the NDMA contamination once they became "knowledgeable".

In this connection, Prinston SOP PRN-3003.03 External Audits effective September 29, 2016 was the fourth revision. (ZHP00114370). This SOP's Purpose: "To assess the effectiveness of supplier's quality assurance systems and to ensure that suppliers meet the requirements of cGMP." Among other things, per 6.7 any deficiencies identified on audit were required to be addressed and remedied by CAPA's, and in 6.9 "Providers who do not meet cGMP requirements and/or fail to correct undesirable conditions will be disqualified."

The presence of the NDMA and NDEA in the valsartan API and finished dose product manufactured with the zinc chloride process and TEA process with sodium nitrite quenching resulted in the sale of drug products that did not match the approved form of the drug products. Thus, the drug products sold containing the contaminated drug product were represented to be something they were not: the approved form of Valsartan. The drug products were adulterated by definition, and thus were not legally permitted to be sold, due to the failure to meet the compendial description of the approved form of the drug product, and the manufacture of the drug products in violation of CGMPs.

The TEA With Sodium Nitrite Quenching Manufacturing Process

In 2011, ZHP changed its manufacturing process for valsartan API, to the process known as TEA with sodium nitrite quenching. I have been provided a translated version of ZHP's change request form (ZHP00063829) indicating that the purpose was to "improve the quality of valsartan and simplify the operation process." Prior, ZHP utilized the TEA process without sodium nitrite quenching, and the valsartan TIN process, neither of which introduced the risk of NDMA or NDEA creation. There is no suggestion of a risk of NDMA or NDEA being formed with either of those prior processes.

The risk assessment for the TEA with sodium nitrite quenching process did not evaluate the potential for the substances used in the manufacturing process to react and form nitrosamines. As described in the July 6, 2021 report of Stephen Hecht, Ph.D., the formation of nitrosamines including NDEA and NDMA as a result of the foreseeable chemical reactions in the process were well understood by organic chemists in the scientific community, and the technical means to test and determine whether nitrosamines were formed (mass spectrometry) were readily available. As set forth below, this was confirmed in the deposition testimony of ZHP witnesses, with reference to scientific literature that pre-dated the development of the TEA with sodium nitrite quenching process (and the zinc chloride process). This is also confirmed in the reports of Dr. Hecht and the report by Dr. Najafi.

The root cause of the NDEA and NDMA impurities is set forth in the ZHP Deviation Investigation Report dated November 5, 2018 (DC-18003, PRINSTON0075797) ("TEA DIR"). ZHP discussed the various pathways for the creation of NDEA in the TEA process on page 50-55, and 61 of 236. In summary, as with the formation of NDMA, ZHP pointed to the three factors required to form NDEA in the final drug substance on 52 of 236:

- Presence of diethylamine in the manufacturing process, such as its presence in quenching step;

- Presence of nitrous acid in the manufacturing process, such as quenching of azide using sodium nitrite;

- The possibility of direct contact between secondary amines and nitrite in the presence of the target product.

Stated another way at 53 of 236: "Trace amount of diethylamine hydrochloride in triethylamine hydrochloride can react with nitrous acid (formed in situ between $NaNO_2$ and HCl) during the quenching of excess azide with sodium nitrite."

Min Li of ZHP confirmed that the presence of NDEA resulted from the manufacturing process: "the DEA [diethylamine] is a typical process impurity of TEA, so DEA would also, yeah, would react with the nitrous acid to perform NDEA." He confirmed that the presence of NDMA resulted from the manufacturing process as well as cross-contamination: "in some of the TEA raw material it may contain a trace amount of, you know, of dimethylamine, okay, so that's one root cause…for some of the, you know, product, they were manufactured, you know, using the share line, you know, with the zinc chloride valsartan." (Min Li 4/20/21 Dep. Tr. 77:8-80:16).

The TEA DIR provides a detailed analysis of the cross-contamination including due to shared production lines and solvent recovery, at 126-135 of 236. With reference to cross-contamination due to shared production lines, the Report states in part on 129-130 of 236, "However, since the probability to generate trace amount of NDMA and NDEA in the Valsartan was not in the scope of understanding until June 2018, consequently, there was no control acceptance limits established for NDMA or NDEA as part of the specifications in cleaning validation and daily cleaning. Therefore, the residual NDMA and NDEA in the equipment after cleaning for process switch were not analyzed….Based on the analysis of the NDMA and NDEA data, the original equipment cleaning procedure applied might not be able to get rid of the NDMA and NDEA residue on the equipment completely." On 138 of 236, the Report states: "no special cleaning and testing control were set in the process of cleaning focus on the trace amount of NDMA or NDEA impurity, it likely had trace amount of NDMA or NDEA impurity remaining in the equipment and resulted in carry-over into other grade of Valsartan." ZHP states at 129 of 236 that "No GMP violation was identified based on the investigation," however this conclusion is completely contradicted by their own analysis, and again illustrates ZHP's refusal to recognize that it deviated from CGMPs in numerous material ways.

The failure to perform a science-based assessment of the processes deprived ZHP of the awareness that NDMA and NDEA could form, which would have required testing of the equipment following cleaning and before its next use, and recovered solvents, as discussed in the next section of the TEA DIR. That testing would have detected the NDMA and NDEA and the contaminated drug products would not have been sold. ZHP's test results also show that some of ZHP's $ZnCl_2$ valsartan was contaminated with NDEA. (ZHP02364173). Each of these root

causes was a result of CGMP violations, including inadequate risk assessment and testing of each contaminated batch during development and process validation, as well as during manufacture and prior to sale of each batch once commercialized, and inadequate cleaning of equipment and avoidance of cross-contamination coupled with inadequate risk assessment and testing of the equipment for NDMA and NDEA prior to sale. Any cross-contamination that occurred due to solvent recovery and was not detected would be in violation of CGMPs for the same reasons. To the extent there were cross-contamination issues with regard to the drug product manufactured with the zinc chloride process the same analysis would apply. ICH Q7, Section VIII.E. Contamination Control states "Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials." Additionally, 21 CFR §211.67(a) Equipment cleaning and maintenance states "Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." Continuing, 21 CFR §211.67(b) states "Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product." The above listed regulations and guidance demonstrate the Agency's requirement for assurance of contamination control. *see, e.g.*, SOP TE-001-1 (ZHP00671809); SOP DB-1096-5; SOP DB-1097-5 (ZHP00373132-373145).

As set forth above, the July 6, 2021 report of Stephen Hecht, Ph.D. explains that the potential chemical reactions in the TEA with sodium nitrite quenching manufacturing process and consequent formation of nitrosamines including NDEA and NDMA were well understood by organic chemists, and the technical means to test and determine whether nitrosamines were formed in the manufacturing process as well as to test for cross-contamination from shared production lines (mass spectrometry) were readily available, long before ZHP began to develop the TEA and zinc chloride processes. This is consistent with the deposition testimony of various ZHP witnesses, as described herein, and the scientific literature they were questioned about.

As stated above, Eric Gu of ZHP confirmed that if the NDMA and NDEA in the valsartan API manufactured with the zinc chloride and TEA process with sodium nitrite quenching had been known it would not have been sold: "If we known that, it shouldn't be sell on the market." (Eric Gu 4/6/21 Dep. Tr. 391:12-394:7, 395:10-397:10).

Also, as stated above, the presence of the NDMA and NDEA in the valsartan API and finished dose manufactured with the zinc chloride process and TEA with sodium nitrite quenching process rendered the drug products adulterated by definition, including because of the failure to manufacture the drug products in compliance with CGMPs.

The Zinc Chloride Process

In 2011, ZHP developed another manufacturing process for its generic valsartan, changing certain substances used in the manufacturing process, including the substitution of

dimethylformamide for trimethylamine, and zinc chloride for toluene in the tetrazole ring formation step, and increasing the quantities of sodium azide and sodium nitrite. The change request form indicated the change was, in part, to increase yield and lower cost. (ZHP01843066 (ZHP 195)). This was confirmed by Jun Du during a meeting with an FDA investigator, where he pointed out that this change allowed ZHP to dominate the world market for valsartan. (PRINSTON00162373).

Valsartan API manufactured with the zinc chloride process was utilized by the finished dose manufacturing arm of ZHP to manufacture finished dose product that was then sold or transferred to ZHP's wholly owned subsidiary Prinston, which then marketed and distributed that finished dose product through its wholly owned subsidiary Solco. It is my understanding that ZHP also sold valsartan API manufactured with the zinc chloride process to Teva which then utilized that API in the manufacture of Teva finished dose valsartan for sale in the United States. (PRINSTON00000001-46; ZHP02364173; Teva 230; Michelle Osmian 5/06/2021 Dep. Tr. 33:2-236:24; 239:7-240:2).

The root cause of the NDMA impurity is set forth in the ZHP Deviation Investigation Report dated July 20, 2018 (DC-18001, ZHP00004363-4471) ("ZNCL DIR"), and is also discussed in the TEA DIR cited above. On page 17 of 33 of the ZNCL DIR, it states, "Based on the previous mechanism analysis, this impurity is probably generated in the quenching process in which the product of the reaction is also present." On page 19 of 33, ZHP stated, "Based on the above elucidated root cause, the presence of trace amount of NDMA in the final Valsartan API requires the convergence of the following three factors: i) use of dimethylformamide (DMF) in the tetrazole formation step, ii) quenching of azide using nitrous acid, and iii) quenching takes place in the presence of the product." These are the same three factors described in the TEA DIR. This is further reiterated on page 22 of 33, including, "It seems clear that NDMA is only formed in Process II (ZNCL) associated with the use of solvent dimethylformamide (DMF) during the quenching of unreacted azide AND in the presence of the product of that step, indicating NDMA is a process impurity in Process II (ZNCL)."

The reports of Stephen Hecht, Ph.D. and the report of Dr. Najafi establish that the potential chemical reactions in the zinc chloride process and formation of nitrosamines including NDEA and NDMA were well understood by organic chemists, and the technical means to test and determine whether nitrosamines were formed (mass spectrometry), were readily available, long before development of that process. This is consistent with the deposition testimony of multiple ZHP witnesses, and the scientific literature they were questioned about.

Of note, the risk assessment for this process does not evaluate the potential for the substances used in the manufacturing process to react and form nitrosamines at any time, including before and after the start of marketing of the contaminated valsartan finished dose due to its manufacture utilizing the contaminated valsartan API. The May 13, 2022 Stipulation by ZHP spells out ZHP's acknowledgement that a risk assessment was required in connection with the process change to the zinc chloride process, and the failure by ZHP to perform any evaluation of the potential degradation/decomposition (terms used interchangeably) of DMF to

form dimethylamine, including the complete failure to perform scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process. The Stipulation also addresses the Change Request Form used to document the steps required by ZHP's internal change control procedure SMP-018 to evaluate and approve the change in manufacturing process, including a quality review to identify impurities due to the new process. The Change Request Form, discussed in more detail below, was dated November 29, 2011 and signed by Luo Ping of Quality Assurance and included a list of action items to be completed going forward (ZHP01843072).

In summary, those actions, including preparation of the process validation protocol, manufacturing of validation batches and preparation of the process validation report, checking and confirmation of relevant equipment in the workshop, completion of method validation and establishment of a stability study protocol for validation batches and start of stability study, and completion by regulatory affairs of the DMF update including submission of the DMF update to regulatory authorities and notification to customers, were documented as completed on December 20, 2013 by Luo Ping.

Annex-1 to the Change Request Form provides detail as to the changes, and indicates that Shanghai SynCores was asked to "optimize the previous synthesis process of Valsartan (Process II, Triethylamine Hydrochloride Process), focusing on the new tetrazole formation process development of crude step." Additional changes were made as well and this is set forth in detail. Specific to the inclusion of DMF, the Raw Materials Changes Comparison indicated, that "The towing operation with DMF is added…Tetrazole formation system: ZnCl, sodium azide and DMF are used instead of triethylamine hydrochloride, sodium azide and toluene. ZnCl and DMF are the new materials. New solvent [MTBE] used for quenching, extraction and saponification." (ZHP01843074-75). The Main Materials Charging and Production Capacity Comparison indicated in connection with the Acylation step, in part that 2) The towing operation with DMF is added. The solvent used for dissolving pentacylated compound is changed from Toluene to DMF." Also increases in the quantities of sodium azide and sodium nitrite during the crude step, and states in part: "1) The tetrazole formation system is changed and the quantity of sodium azide is increased; 2) Sodium azide [should be sodium nitrite] used for quenching is increased due to the increase of sodium azide; 3) The concentration of sodium hydroxide for saponification is increased and material usage is increased accordingly; 4) The quantity of HCl solution and ethyl acetate is increased due to the improvement in yield." (ZHP01843075-76; Certified Translation of ZHP00000171). Table 3-4 Comparison on specification of Valsartan (US specification) indicated no changes except with regard to the solvents, stating, "The solvents of DMF and MTBE are new added in ZnCl process, and both of them are added in the specification of residual solvents." (ZHP01843084-85). Further detailed analysis is included.

Annex-1 includes a section titled: 7.3.3 Conclusion of Risk Assessment. This stated in part: "**After evaluation, this change has a lower risk in terms of quality and safety**. In terms of quality, the quality of valsartan before and after the change can be compared according to the existing analysis method when the new process is validated, and the quality consistency can be evaluated." The Conclusion section stated in part, "Through a large number of experimental

results about optimizing process and combined with theoretical analysis, the synthesis route of new process and critical process parameters are initially determined by Huahai, and **the preliminary analysis and evaluation of impurities in new process is completed, confirming that the quality of product risk is controllable**…The changes of original process are applied and the new process validation is organized." (ZHP01843099). **On April 4, 2012, Jucai Ge, QA manager, signed off to confirm "Approval of GMP compliance**." (ZHP01843104).

Included following Annex-1 is a Change Request form signed by Lucy Liu, Manager of Regulatory Affairs, on January 17, 2012. This form incorrectly described the change as a "Minor change," contrary to the Change Request Form which described the change as a "Critical Change." In addition, it stated (incorrectly), "Synthetic route, intermediates remain the same and **no adverse change in qualitative and quantitative impurity profile…Drug substance quality meet the unchanged specification compared to the approved process data as *Annex-2***." (ZHP01843116).

The DMFs and ANDAs

I have reviewed the applicable DMFs. According to the TEA DIR at 57-58 of 236:

- The DMF for the TEA process (without sodium nitrite quenching) was filed with USDMF registration number 23491. The date is not provided in the TEA DIR, but the filing date of January 22, 2010, is confirmed at PRINSTON00000005.

- The DMF for the TEA process with sodium nitrite quenching was filed in April 16, 2012. The USDMF registration number is not provided there, but is confirmed to be USDMF registration number 23491 at PRINSTON00000005.

- The DMF for the zinc chloride process was filed in December 2013 with USDMF registration number 23491.

The ANDAs filed by Prinston on September 13, 2012, and August 26, 2013, respectively, referenced USDMF registration number 23491, and listed the impurities found with that process, not including NDMA or any other nitrosamine. (PRINSTON00000012; ZHP01451842, -874; PRINBURY00058078; PRINBURY00058083; PRINSTON00037968, -972; PRINSTON00183155; PRINSTON00177677).

On December 10, 2013 ZHP submitted its Technical Amendment to Valsartan USP (Process II), DMF# 23491 to the FDA DMF Staff, for the change to the zinc chloride process, indicating in part the substitution of zinc chloride in step 4, and "in step 3 and step 4, DMF and MTBE are added to facilitate the process and will be successively removed." (ZHP01713711). The Amendment to Drug Master File dated December 10, 2013 (PRINSTON00073102) states on page 11/16: "There is no adverse change in qualitative and quantitative impurity profile, the process change/optimization does not impact the drug quality." In addition, on page 15/16, "So far there are two workshops are used for Valsartan production based on currently optimized

process at the same site followed the same CGMP and Quality system in full conformity with parts 21 CFR part 210 and 211. The proposed process is equivalent in all the 2 workshops and charged materials are scalable in quantity. The change does not affect the reproducibility of the production and the specification of intermediates & the final substance remains the same."

Module 3.2.S.3.2 of the zinc chloride DMF dated November 10, 2013, titled Impurities (HUAHAI-US00007752), indicates on page 147 of 172 that the application of the "FDA draft guideline *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* is applicable to the applications for existing active substances." The Module unequivocally states on pages 148-149 of 172 that all of the potential impurities were evaluated, no "high potency genotoxic" N-nitroso- compounds are among the impurities, and the impurities pose "no genotoxic risk in Valsartan." The same is stated with regard to residual solvents. This information regarding impurities was incorrect, due to the CGMP deficient risk assessment.

Similarly, Module 3.2.S.3.2 of the TEA with sodium nitrite quenching DMF dated January 20, 2012, titled Impurities (PRINSTON00080011; PRINSTON00079747; PRINSTON00071532), indicates on page 108 of 133 that the application of the "FDA draft guideline *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* is applicable to the applications for existing active substances." The Module unequivocally states on pages 109-110 of 133 that all of the potential impurities were evaluated, no "high potency genotoxic" N-nitroso- compounds are among the impurities, and the impurities pose "no genotoxic risk in Valsartan." This information regarding impurities was incorrect, due to the CGMP deficient risk assessment.

The ADNAs filed by Prinston referenced the DMF number 23491, and listed the drug formulations and impurities, with no mention of NDMA or NDEA. (PRINSTON00000012; ZHP01451842, -874; PRINBURY00058078; PRINBURY00058083; PRINSTON00037968, -972; PRINSTON00183155; PRINSTON00177677). Thus, the ANDAs were approved to allow the sale of valsartan that was not contaminated with, and did not otherwise contain the genotoxic impurities NDMA or NDEA. That is what was represented as being sold. Yet, valsartan contaminated with NDMA/NDEA is what was sold and introduced into interstate commerce.

As a result, ZHP and those in its supply chain did not sell the approved form of valsartan because the approved description of valsartan did not include the presence of NDMA or NDEA. As set forth herein, proper application of CGMPs at any stage of the lifecycle would have been easily accomplished and would have resulted in identification of the NDMA and NDEA, and would have prevented the sale of the contaminated drug products. Mr. Iozzia confirmed in his deposition that ZHP had internally recognized that CGMPs were applicable throughout the lifecycle of the products it sold, discussing a powerpoint that stated, "Huahai commits that quality is our life. Employs quality practices during the whole life cycle of products. Meets and exceeds the regulatory agency's requirement…Huahai uses high quality standard and adopts continuous quality improvement and innovation strategy to ensure strict scientific and systematic quality management system," and also confirmed "this is something that your

company has always represented to other companies and the public, that this is how your company conducts its quality operations…". (John Iozzia 1/20/21 Dep. Tr. 86:10-90:11). These aspirational statements correctly described ZHP's CGMP duties, ongoing for the drug product's lifecycle, however the documents provided demonstrate that ZHP did not meet these standards.

In July, 2018 ZHP submitted an Amendment to Drug Master File, to modify the zinc chloride process, by extracting the product before quenching the sodium azide, in order to eliminate the risk of NDMA contamination. (ZHP00097775, ZHP00097777). Section 2 indicates "The purpose of this technical amendment is to provide the quality control of newly identified genotoxic impurity N-Nitrosodimethylamine (NDMA) in the specification of final drug substance." The optimization is described (at ZHP00097782) as, [redacted] As stated above, ZHP could have done this from the start, or once they began to manufacture and sell the drug product.

Deposition Testimony

I have been provided the deposition transcripts of a number of ZHP employees. This testimony provides relevant context and detail, which I have considered and relied on in understanding what occurred and forming my opinions. This includes the following, which summarizes significant information provided;

Eric Gu:

Eric Gu was deposed on April 5-6, 2021. He was the President/General Manager of Shanghai Syncores since February, 2014. The function of Shanghai Syncores, which was apparently owned by ZHP, is described in a PowerPoint dated in July, 2013. (4/5/21, 49:17-56:3). Mr. Gu provided testimony including but not limited to:

Shanghai Syncores developed the valsartan manufacturing process using zinc chloride and sodium nitrite quenching, at the lab scale. (4/5/21, 60:6-10).

A scale up process from lab scale to pilot scale to commercial scale was required by good manufacturing practices, and the risk assessment process was supposed to be implemented throughout the development process, from lab scale to pilot scale to commercial scale. (4/5/21 Dep. Tr., 39:13-45:3). This was not done by ZHP.

The contract between Syncores and ZHP provided that Syncores would be responsible for the process development, refers to successful test of the process "in the pilot scale," and only

ZHP had the facilities and equipment sufficient to conduct pilot scale testing. Of note, the document did not "specifically address genotoxic impurities." (4/5/21, 101:12-108:15). The document also provided that one of the parameters to be met by Syncores was to develop a process where "The purity and content of the final product sample" provided by Syncores…"shall meet the quality standards of the valsartan process…" which were set by ZHP. The process was not supposed to create valsartan containing NDMA. (4/5/21, 110:11-111:18, 128:17-20).

Syncores completed its work and reported the outcome to ZHP on January 20, 2011. (4/5/21, 139:10-23).

Shanghai Syncores and ZHP were required to conduct a genotoxic impurity analysis when they developed the zinc chloride process, and were aware of the FDA guidance titled "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" dated December 2008. (4/5/21, 58:15-60:4).

In connection with the FDA Guidance titled "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" dated December 2008, Mr. Gu confirmed that as a matter of risk assessment both ZHP and Syncores were responsible to know in 2011, as set forth in Section 4-A titled "Prevention of Genotoxic and Carcinogenic Impurity Formation," that, "Since drug-related impurities presumably provide limited, if any, therapeutic benefits and because of their potential to cause cancer in humans, every feasible technical effort should be made to prevent the formation of genotoxic or carcinogenic compounds during drug substance synthesis or drug product manufacturing." (4/5/21, 69:1-70:23).

Despite the FDA Guidance, Mr. Gu stated that no genotoxic impurity analysis would be performed unless the impurity was known/suspected – "When you know, you will do the analysis. If you don't know okay, you will not." (4/5/21, 60:11-61:5). This is a flawed approach. It is recognition of the potential formation that triggers the obligation to test.

When asked to confirm the importance of "identification of the potential impurity…as part of the risk assessment," Mr. Gu repeated that they could not look for something they did not know was present, and did not respond when asked to confirm that if they did not know because of "an inadequate evaluation of potential impurities, then you have violated good manufacturing practices." (4/5/21, 62:22-63:11).

Despite stating that the potential chemical reaction was not known, Mr. Gu acknowledged that the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" stated in part: "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA." (4/5/21, 65:3-65:24).

Mr. Gu could not identify anybody at Syncores who "evaluated potential degradation of DMF as part of the zinc chloride process" during the development of the zinc chloride process. (4/5/21, 77:21-78:10).

A July 2013 PowerPoint about Syncores addressed, "Analytical Capabilities" including "Identification of impurity, structure elucidation," which he stated addresses "to identify impurity could be found in the process or in the APIs or even in the intermediates," including the identification of impurities resulting from side reactions, which "requires an analysis of the chemical reactions," both the main reactions and side reactions. He agreed that "Good manufacturing practices requires evaluation of the main reactions and the side reactions." (4/5/21, 83:9-85:9). In this context he also agreed that the reaction between dimethylamine (DMA) and nitrous acid that formed NDMA was a "chemical reaction." (4/5/21, 86:10-87:4). These evaluations did not occur, in violation of CGMPs.

Mr. Gu discussed the EMA guidelines titled "Guideline on the Limits of Genotoxic Impurities" in effect from January 1, 2007, to January 31, 2018, confirming that Syncores was aware of this guideline, and that he supposes ZHP, which owned Syncores and in a sense was his employer as well. He then discussed Section 4, titled "Toxicological Background," which provided in part that "According to current regulatory practice, it is assumed that in vivo genotoxic compounds have the potential to damage DNA at any level of exposure and that such damage may lead/contribute to tumor development…Thus, for genotoxic carcinogens, it is prudent to assume that there is no discernible threshold and that any level of exposure carries a risk." Also, that "some structural groups" including n-nitroso compounds including NDMA and NDEA, "were identified to be of such high potency that intakes even below the threshold of toxicological concern, or TTC, would be associated with a high probability of a significant carcinogenic risk…this group of high potency genotoxic carcinogens…have to be excluded from the TTC approach. Risk assessment of such groups requires compound-specific toxicity data." He confirmed that both Syncores and ZHP were aware of that information when developing the zinc chloride process and TEA process with sodium nitrite quenching. (4/5/21, 90:6-97:16).

Per that EMA Guideline, the first step was a risk assessment that "is supposed to identify the existence of the impurity." Next, the risk assessment required analysis of the risk to determine the risk posed by the identified impurity. (4/5/21,159:15-162:22).

Mr. Gu confirmed that ZHP "would have been aware these guidelines were put out in 2007 and ZHP would have known as of 2007 that nitrosamines, including NDEA and NDMA belonged to a class of very potent genotoxic carcinogens as of that time in 2007," which per the Guideline required control "as low as reasonably practical," as opposed to according to the threshold of toxicological concern. (4/6/21,381:6-386:21).

Mr. Gu testified with regard to a 2009 article published in the scientific journal Tetrahedron Letters, titled: DMF, Much More Than a Solvent. The article indicates in part that "DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of acidic or basic materials.." He confirmed that it was known in the chemistry community that under certain circumstances DMF could decompose to yield dimethylamine. (4/5/21,172:13-174:9, 183:12-21).

Mr. Gu confirmed that the root cause for the formation of NDMA in the valsartan API manufactured with the zinc chloride process was in part attributable to the degradation or decomposition of DMF to yield dimethylamine, and the reaction of nitrous acid with the dimethylamine. (4/5/21, 178:24-181:4).

Mr. Gu confirmed that Syncores did not evaluate the potential decomposition of DMF into DMA as part of the zinc chloride process. (4/5/21, 98:17-99:5). When asked if it would have been reckless for ZHP and Syncores not to test to try to identify potential nitrosamine impurity if they knew of the potential creation of a nitrosamine in the manufacturing process, Mr. Gu stated that they were required to "do the thorough studies, do the entire risk assessment to get that out of the process, get that impurity out – under control in the final drug, APIs" if they knew or suspected. (4/5/21,1207:14-208:6). They should have known of these potential reactions and tested as a result.

Mr. Gu also testified with regard to the "unknown peaks" that were seen on routine gas chromatography by ZHP and some of its customers. He confirmed that an unknown peak should be investigated by ZHP, but could not provide any specific reason why Novartis discovered that the unknown peak at issue indicated the presence of NDMA, before ZHP, focusing on his assertion that "it was not so easy to detect" and "it's quite a challenging work." (4/5/21,210:24-219:5, 236:24-237:8).

Mr. Gu was not aware that ZHP customer Sun Pharmaceuticals complained of unknown peaks in November 2016, and was not aware that, according to the European Medicines Agency, ZHP did not directly compare the unknown peaks observed by Novartis to ZHP's own gas chromatography. Nor was he aware that Novartis had shared its GC-FID method for evaluating chromatogram peaks with ZHP in July 2017. (4/5/21, 240:3-243:18).

Mr. Gu was also asked about the finding by the European Medicines Agency that, "contrary to what the company [ZHP] stated in their retrospective analysis of the process change, the core principles of ICH Q8, Q9, and Q10 were not considered, and potential impurity profiles and associated risks were not addressed by the R&D laboratory [Syncores]." When asked if he agreed with that finding, Mr. Gu stated, "Okay. Yes, at 2018 looking back to the 2010 or 2011, you can make all those comments," but then pointed to the European approval of the process, inspections of ZHP, and questioned whether those ICH provisions were "out there in 2010 or 2011." However, he agreed that, "looking back, now, yes, you can say that," as a result of the failure to apply the core principles of those ICH provisions, "potential impurity profiles and associated risks were not addressed by the research and development laboratory [Syncores]." (4/5/21, 244:3-247:9).

With regard to the dates on which the above cited ICH provisions were in effect, Mr. Gu agreed on further questioning that ICH Q8 titled: Pharmaceutical Development, was in effect in 2008; ICH Q9 titled: Quality Risk Management, was in effect in 2005; and ICH Q10 titled: Pharmaceutical Quality System, was in effect at least as of 2008. (4/5/21, 253:10-255:16).

When asked why, according to him, despite every batch showing the "NDMA peak just after the Toluene peak on the chromatograms. . . nobody at ZHP realized that it needed to be tested and identified," Mr. Gu stated that ZHP was aware of these peaks and "did whatever they can," but ultimately that, "They are struggling, I guess, in the past." (4/6/21, 333:21-335:19). This is an admission of the inadequate risk assessment/management with regard to the unidentified peaks.

When asked if ZHP should have evaluated the NDMA peak as soon as it was seen on testing, and whether that was required as a matter of CGMP, he was unable to provide an answer. (4/5/21, 232:23-233:20). In my opinion, that evaluation was required and the failure to do so constituted a violation of CGMP because it was unacceptable for ZHP to ignore this indication of an unknown impurity, especially in light of the scientifically known potential for creation of nitrosamines. This is true as to every batch manufactured.

Mr. Gu was also asked about ICH Q3A, which was in effect as of 2006, and confirmed that the ICH Guidelines provided, "very important principles that guided the development process." He confirmed that Section 3.1 required ZHP, to summarize the actual and potential impurities: "This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products." In this connection, he agreed that, "Dimethylamine was a possible degradation product of DMF as used in the zinc chloride process." (4/6/21,354:17-358:2). Based on the report of Dr. Hecht, and the testimony of ZHP witnesses confirming that the chemical reactions at issue were known in the scientific community well before the development of the TEA process with sodium nitrite quenching and the zinc chloride process, "a sound scientific appraisal of the chemical reactions involved in the synthesis" was not performed.

Mr. Gu confirmed that ZHP was obligated to update the valsartan API impurity profile with the FDA and European authorities. "You have to update the impurity profiles once you gain more knowledge." (4/6/21,330:18-332:11). This is in line with the ongoing CGMP obligations since this could and should have been identified every day from start of development to the end of marketing of the drug.

Mr. Gu was also questioned about the November 29, 2018 FDA Warning Letter, which found in part that ZHP, "failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. . . Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine." He agreed that NDMA was a probable human carcinogen, but stated, "In 2011, okay, we didn't know. We didn't know that there were probable human carcinogens like NDMA or NDEA in the product." However, in this context, Mr. Gu agreed that, "ZHP was responsible for the quality of the valsartan that it manufactured," and "Yes, you know, ZHP is responsible for the API they are making." (4/6/21, 360:8-374:12).

He also agreed with the Warning Letter, which stated that if new or higher levels of impurities were detected, ZHP was responsible to, "fully evaluate the impurities to take action to ensure the drug is safe for patient[s]." (4/6/21,375:16-376:11). This is yet another acknowledgement of the fundamental ongoing CGMP obligation to conduct ongoing risk assessment/risk management on the drug product.

Mr. Gu confirmed the NDMA levels for the zinc chloride process as stated in a September 1, 2018 letter to the FDA, including NDMA levels measured in various batches of 148.2, 158.8, 167.3, and 188.1 parts per million. (4/6/21,387:14-390:19).

Mr. Gu confirmed that, "If we knew, okay, there's NDMA in the valsartan, you know, ZHP wouldn't sell that," and as a matter of evaluation of the health or safety issues at the levels of NDMA shown on the testing, ZHP stopped selling and recalled all the pills containing NDMA. (4/6/21, 391:12-394:7).

Mr. Gu confirmed the same with regard to the TEA process with sodium nitrite quenching, which created NDMA and NDEA due to the sodium nitrite quenching during the manufacturing process, "If we known that, it shouldn't be sell on the market," for the same reasons as with the zinc chloride process. (4/6/21,395:10-397:10).

Mr. Gu confirmed that ZHP first told the FDA that the zinc chloride process was creating NDMA on July 9, 2018. (4/6/21,397:17-399:1). He also confirmed that the FDA was notified of the root cause of the NDMA, "the solvent dimethylformamide was introduced and its impurity/degradant…dimethylamine, unexpectedly reacts with nitrous acid generated in situ between sodium nitrite and sodium hydrochloride during the subsequent quenching step in the presence of that product of that step." (4/6/21,400:3-24).

Mr. Gu confirmed that after the disclosure to the FDA, ZHP modified the manufacturing process, and, "ultimately your solution was to quench the azide separate from the product so it wouldn't become contaminated with the NDMA," and as a matter of quality management going forward, "GC-MS would be used to evaluate all peaks to make sure that they were not genotoxic impurities that needed to be controlled out of the product." (4/6/21, 455:1-458:15). These steps could have been taken from the start, as the potential chemical reactions and means to test were known and available.

Peng Dong:

Mr. Dong worked in the ZHP Technical Department as Deputy Director, which was responsible, "to improve and upgrade the manufacturing process for the products under our management." (3/29/21, 27:18-31:13). This was an ongoing quality duty.

He confirmed that the internal protocol titled: Guideline for Genotoxic Impurity Evaluation (No. API-R&D-002) (bates ZHP01447235-242), Section 2, provided that, "All intermediates and APIs produced under GMP conditions must be identified for genotoxic

impurities," and per ICH the risk assessment evaluation included identification of genotoxic impurities and confirmation of the quality specifications of any API, including valsartan. (3/29/21, 33:9-34:10). This would have applied to every manufactured batch of API.

He confirmed that Section 4.2.1 indicated that, "Sources of genotoxic substances include raw materials, reagents, solvents, intermediates, and by-products." (3/29/21, 34:22-35:4).

He confirmed that Section 4.2.3 indicated that, "After product pilot, genotoxic impurities should be preliminarily determined and included in the development report." (3/29/21, 41:14-42:1).

He confirmed that Section 4.2.4 indicated that, "The identification of genotoxic impurities should include confirmed structure of genotoxic impurities and confirm analysis method and residual limit of the impurity." (3/29/21, 42:3-11).

He confirmed that Section 4.3.1 indicated that, "The technical department organizes relevant departments to evaluate all raw materials, reagents, solvents, intermediates, and by-products of the product and evaluate whether they contain genotoxic substances." This applied to all technical departments at ZHP including within the Chuannan facility. (3/29/21, 42:13-43:4, 44:7-45:21).

He confirmed that Section 4.4.1 indicated that, "Genotoxic substances are potentially destructive to DNA at any intake level, and this damage may lead to tumors." (3/29/21, 45:23-46:11).

He confirmed that Section 4.4.11 indicated that, "Genotoxic impurities and their residual limits as found by the company are found in Appendix A." He also confirmed that the process change for valsartan was conducted, "based on the ICH and SOP requirements at that time." The questioning indicated that the document had been modified on June 17, 2011 (pre-dating the process changes to the TEA process with sodium nitrite quenching and the zinc chloride process). When asked whether this guideline was applied during the work performed in connection with the zinc chloride process change, he could not say for sure but reiterated that, "we conducted the corresponding work based on the requirements of ICH then and the requirements of SOP then." (3/29/21, 46:13-50:12, 54:1-55:18, 61:2462:16).

Mr. Dong was questioned about the Change Request Form for the zinc chloride process, indicating that the change was to "use zinc chloride as catalyst." (3/29/21, 64:23-65:9, 69:3-17). He confirmed the purpose for the process change to increase conversion to crude product and the "major changes from the original TEA process to the zinc chloride process for valsartan," which involved, "changes in the reagents, reaction temperatures and other parameters." This involved the use of zinc chloride, sodium azide, and DMF, "to alternatively replace the original triethylamine (TEA), sodium azide, and toluene." As described in more detail herein, he also confirmed that all of the changes needed to be evaluated by a risk assessment for new potential

risks, "for the change procedure, including materials and other parameters change." (3/30/21, 186:6-189:15).

The Raw Materials Change Comparison attached to the Change Request Form indicated that the quantity of sodium azide was more than doubled (from [redacted] kg to [redacted] kg) with a corresponding increase in the quantity of sodium nitrite used for quenching the sodium azide ([redacted] kg to [redacted] kg), and in the Acylation section indicates that DMF was added to the process. When asked if ZHP was required to evaluate these substances for impurities Mr. Dong confirmed that ZHP was required to comply with "the requirements of ICH and SOP," and he gave the same answer when asked to confirm that ZHP was, "required to perform a risk assessment for potential impurities resulting from these changes in the substances used to manufacture valsartan." (3/29/21, 102:20-103:21, 104:5-105:4, 105:9-107:10, 107:14-109:1). However, ZHP only evaluated the amount of residual sodium azide and sodium nitrite based on the increased quantities of both. (3/30/21,220:14-223:1).

The zinc chloride Change Request indicated this was a critical change, not a minor change. (3/29/21, 70:11-18, 71:15-72:1). As a result, the regulatory affairs section of the document provided that, "CEP major changes procedure would be applied." (3/29/21, 78:16-79:4).

The Change Request was dated November 27, 2011, confirming that the change request was approved and that the next step was process validation, described by Mr. Dong as, "Process validation is one of the managed activities under GMP." (3/29/21, 75:14-76:14). The quality control department section required that, "The residue of zinc chloride and residue of solvents used in the process need to be tested for quality review. The relevant method validation should be completed." (3/29/21, 76:16-77:5). However, due to the inadequate risk assessment that failed to identify the potential formation of nitrosamines during development and then thereafter through the commercial marketing, the process validation testing failed to include testing for nitrosamines, constituting a CGMP violation.

Mr. Dong confirmed that the "lab research report," dated January 20, 2011, prepared by Shanghai Syncores was "the basis to develop the zinc chloride process," and provided for the need to further evaluate the zinc chloride process at the pilot scale, which is "To confirm whether the process parameters have been reasonably determined, including further optimization of the process." (3/30/21, 201:4-15, 203:5-206:1, 208:3-209:4). No pilot scale was conducted, which was a violation of ZHP's internal SOPs (PRINSTON00162369), and CGMP.

Mr. Dong confirmed that ZHP was required to comply with CGMP with the process change. The quality assurance section of the Change Request required compliance with CGMP: "Evaluate if it against CGMP code; (if so, describe the article and reject it)," and the No box was checked indicating it was not against CGMP code. (3/29/21, 79:7-19, 82:4-17). This is yet another example of the unreliability of ZHP's documentation confirming CGMP.

He confirmed that the Change Action List at Attachment 2 to the Change Request set forth the actions required of each department, per ZHP's SOPs, including, "regulatory affairs updates the DMF and notifies customers and authorities." The document confirmed this occurred on December 20, 2013, "regulatory affairs completed the update of the DMF document and submitted it to the authority, in addition to notification to the customers." (3/29/21, 87:23-88:17, 90:1-12).

Mr. Dong confirmed that SMP-018.01 dated June 15, 2011 (ZHP00469139 (ZHP 196)) was the internal SOP applicable to process changes, and governing and implementing the Change Request Form, with the template attached to the SMP. (3/30/21, 125:6-24, 133:13-134:18, 149:5-13).

Section 1 of SMP-018.01 describes the purpose of the SMP (Standard Management Procedure), including, "to ensure that all the changes that will impact the quality of products will be effectively controlled, " and, "strictly control any change handling that's related to product quality and manufacturing conditions in order to ensure compliance to CGMP, EHS and ICH Q7 requirement, including the change initiation, assessment, approval, implementation and close in order to avoid error or quality incident." (3/30/21, 126:1-127:15). Similarly, Section 3.1 confirmed application of the SMP to "Any changes related to the product quality," and Section 6.1.1 provided "All planned changes to manufacturing processes, GMP equipment, GMP automated systems or GMP facilities must be evaluated to determine any impact to product quality and EHS." Mr. Dong defined product quality as "The product quality was formulated based on the ICH requirement for the API's quality specifications, which was then approved by the FDA." (3/30/21, 134:22-136:17, 139:7-14). In this connection, a critical change (as this change was designated in the change request form for the zinc chloride process) was defined in Section 6.2.1 as, "A change which has direct or potential impact on product identity, strength, quality, purity and regulation, or have impact on validated Procedure, method, qualification of equipment." (3/30/21, 143:141-144:11). Mr. Dong confirmed that the evaluation of potential quality or purity issues with introducing DMF into the zinc chloride process was conducted by the technical department, quality assurance department, quality control department, including personnel with a chemistry background. He also confirmed that testing was performed for residual DMF, but could not tell whether anyone evaluated the potential decomposition products of DMF, and pointed out that some impurities were evaluated (per the change request form potential decomposition/degradation products of DMF were not evaluated). (3/30/21, 153:24-155:19, 156:7-158:7).

Section 6.1.5 provided that, "Each change request is to consider the potential impact to related change control systems and risk assessment," and "The risk assessment includes whether the change control will cause any new risks and these risks will be controlled or eliminated by the suitable preventative action." When asked if a new impurity would constitute a new risk he indicated, "we conducted comparison of the impurities based on the ICH requirement as well as our knowledge at that time." (3/30/21, 139:15-140:24). Mr. Dong confirmed that ZHP was required to perform the risk assessment described in Section 6.1.5, stating, "we conducted a risk assessment based on the SOP requirement and our knowledge at that time." (3/30/21, 141:1-8).

Mr. Dong did not know of the existence of published literature in 2011 indicating that DMF could decompose and create dimethylamine as part of the zinc chloride process, and admitted that in 2011 ZHP, "did not know whether DMF could decompose in the zinc chloride process for valsartan." The most he could say is that "Maybe an idea popped into someone's mind momentarily" or "it could be that suddenly someone dreamt about the scene." (3/30/21, 161:8-17, 162:7-18, 163:15-23, 164:11-165:7, 166:13-167:6). This lack of knowledge was confirmed in the stipulation signed by ZHP. ZHP's risk assessment also failed to evaluate, "how nitrite or nitrous acid might react with dimethylamine during the zinc chloride process," and Mr. Dong admitted this was because, "ZHP did not have an understanding on the creation of nitrosamine impurity in the valsartan products," also pointing to lack of understanding by the authorities and industry, which is an invalid rationale to excuse this serious inadequacy in the risk assessment (see below). (3/30/21, 225:21-226:6, 227:1-7).

ZHP's risk assessment was limited to evaluation of DMF, "DMF was treated as a new impurity." ZHP could produce no documentation of any testing in 2011, "to find out whether DMF could…decompose or not during the zinc chloride process for valsartan." (3/29/21, 167:7-168:19). The table of impurity evaluation at section 7.2.1.2 of the Change Request Form actually confirms that, "Dimethylamine is not listed as a potential impurity that was evaluated." (3/30/21, 213:10-22, 214:18-22, 215:19-216:19, 218:2-9). Further, Mr. Dong confirmed that "ZHP never assessed how nitrite or nitrous acid might react with dimethylamine as part of the zinc chloride process to manufacture valsartan between 2011 and June 2018." (3/30/21, 227:1-70). Mr. Dong discussed the zinc chloride process including the use of DMF as a reaction solvent "to dissolve raw materials during the reaction," and confirmed that ZHP did not do any investigation into the potential for DMF to decompose and yield dimethylamine until June 2018." (3/31/21, 241:3-256:17). As stated throughout my report, this was an ongoing violation of CGMP, repeated with the manufacture of every batch through the end of the lifecycle of that process, and the same holds true for the TEA with sodium nitrite quenching process.

Mr. Dong was shown an article published in 2009 in the scientific journal Tetahedron, which discussed the decomposition of DMF to yield dimethylamine, but could not point to or document any literature search regarding DMF performed by anybody at ZHP. (3/30/21, 169:20-176:7).

Section 6.1.7 provided for discontinuation of the change in manufacturing process, "if upon implementation the process fails to perform within established critical process parameters, fails to meet critical quality attributes, or is unable to meet validation acceptance criteria required to support the change. The change procedure must be restarted and reassessed if necessary." This means that the change must be stopped, per Mr. Dong. (3/30/21, 141:16-143:9).

ZHP's internal operating procedure SMP-018.01 implemented the ICH requirements, including Section 6.1.7, which provided for discontinuation of the change in manufacturing process, "if upon implementation the process fails to perform within established critical process

parameters, fails to meet critical quality attributes, or is unable to meet validation acceptance criteria required to support the change. The change procedure must be restarted and reassessed if necessary."

Mr. Dong confirmed that the risk assessment for the zinc chloride process for valsartan, "did not identify the potential risk of nitrosamine impurity in valsartan." (3/30/21, 191:12-18). He also confirmed that in 2011 ICH Q3A required ZHP to "conduct a sound scientific appraisal of the chemical reactions involved in the synthesis" and potential resulting impurities to establish appropriate quality standards including accurate impurity profile and specifications, yet ZHP's risk assessment failed to identify scientific literature "that would address the decomposition of DMF" and inaccurately concluded that the zinc chloride process had "a lower risk in terms of quality and safety." (3/31/21, 277:2-306:19). In my opinion, ZHP failed to comply with SMP-018.01, and the consistent ICH requirements, in failing to ensure product quality due to an inadequate risk assessment that failed to account for the potential creation of nitrosamines. This occurred during and after development, on an ongoing basis.

Mr. Dong was asked if ZHP ever detected the presence of NDMA in the zinc chloride process API before it went to market and he replied that "regardless whether it was the authorities or the industry or ZHP, no one had any knowledge of nitrosamine in valsartan, including the analytical method." (3/30/21, 132:16-133:9). This response, which is a major theme of ZHP's explanation for why the NDMA was not detected, including responses to the FDA's findings (see below), misses the point. As set forth in the FDA's response to this assertion, the FDA rejected ZHP's explanation and made clear that it was ZHP's responsibility to ensure the quality of its API. As admitted by ZHP, ZHP was responsible for the quality of the API it was manufacturing and selling, and the reason why the presence of NDMA was unknown was ZHP's failure to conduct an appropriate CGMP compliant risk assessment, which would have required testing for nitrosamines with available technology (See Dr. Hecht report and ZHP witness testimony regarding use of mass spectrometry to identify nitrosamines), and that testing would have disclosed the presence of the NDMA. The same analysis and conclusions holds true for the NDMA and NDEA impurities in the valsartan API manufactured with the TEA process with sodium nitrite quenching.

Mr. Dong also confirmed that the December 10, 2013 DMF amendment for the zinc chloride process represented that "There is no adverse change in qualitative and quantitative impurity profile, the process change/optimization does not impact the drug quality." However, he confirmed that the three validation batches for the zinc chloride process were confirmed in the July 20, 2018 DIR for the zinc chloride process and shown to NDMA levels of 53.3, 51.6m 76 ppm," and admitted this was due to the fact that from 2011-June, 2018, "ZHP did not have any understanding regarding the generation of NDMA in valsartan zinc chloride process." (3/31/21, 322:15-340:22). This flawed the process validation, and was due to the inadequacy of the ongoing risk assessment, and the same holds true for the TEA with sodium nitrite quenching process. This is yet another example of internal ZHP CGMP compliance documentation providing misleading and inaccurate information.

He also confirmed in the context of the DMF amendment that the applicable "laws and regulations" including the January 1, 2007 EMEA CHMP guideline applicable to genotoxic impurities, and required "the risk assessment on genotoxic impurities." This included the proviso that "for genotoxic carcinogens it is prudent to assume that there is no discernible threshold and that any level of exposure carries a risk…Risk assessment of members of such groups require compound-specific toxicity data." (4/1/21, 357:19-374:15). The EMA guideline also provided that "as low as reasonably practical guidelines" would not apply to "a structure of very high concern; for example, N-Nitroso compounds," however he could not say that the person responsible for the risk assessment "paid attention" to this provision. (4/1/21, 378:17-385:16).

Mr. Dong also confirmed that the same guideline applied to the TEA with sodium nitrite quenching process risk assessment conducted in 2011 as well. (4/1/21, 374:16-376:20).

In addition, the risk assessments also were governed by the FDA draft guideline "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches." (4/1/21, 377:13378:7, 385:23-396:6). Despite application of this guidance, NDMA was identified as an impurity in the DMF amendment despite scientific literature such as the 1978 IARC Monograph cited herein, clearly setting forth the risk of NDMA from the applicable chemical reactions. Mr. Dong could not say that ZHP was aware of the IARC Monograph. (4/1/21, 396:11-404:1). Similarly, he could not say whether ZHP was aware of the article published December 16, 2009 by people at Beijing University of Technology discussing the formation of NDMA from degradation products of triethylamine, despite the ICH requirement to perform "a careful scientific analysis in performing its risk assessment for impurities." As set forth herein, a draft DIR acknowledged that insufficient research was performed by ZHP. (4/1/21, 446:2-465:9). Mr. Dong did confirm that ZHP was required to reference scientific literature in performing the risk assessment. (4/2/21, 480:10-481:12).

In discussing the Risk Analysis in the TEA DIR, ZHP acknowledged that the risk of the creation of DMF in the zinc chloride process was high as "DMF is easy to be decomposed in dimethylamine (DMA) under the high temperature and acid base condition," and the risk is assessed as high, and states "Product quality will be seriously impacted." (4/2/21, 479:8-480:12, 485:7-490:22). The failure to recognize and address these issues was found to be a CGMP violation, including once the process was put into use: "you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process…. (4/2/21, 492:22-493:18).

Mr. Dong was also asked about the process validation that was established, as to which he agreed "no testing for NDMA impurity was done for those validation batches." The validation batches, which were inadequately tested in violation of CGMPs, were tested in 2018 and showed high levels of NDMA contamination as set forth above. (4/2/21, 480:10-481:12, 508:20-534:4).

Mr. Dong testified with regard to the varied NDMA levels seen in the valsartan API produced in the East and West zones at Chuannan, and addressed the discussion in the TEA DIR as to the factors impacting the NDMA levels, including, "number 1, temperature when adding

sodium nitrite; number 2, charging speed of hydrochloride acid; number 3, ph control at the end; and number 4, aqueous phased separation time during quenching." Further, ZHP confirmed that there was "a lack of detailed description in the production processes." And "Due to the inaccurate description of some of the parameters in the process, there might be likelihood of fluctuation between different workshops or different batches manufactured in the same workshop, which eventually led to the difference in the amount of residual impurities…the residual amounts of NDMA in valsartan API batches." (4/2/21, 536:7-543:2). These unaccounted for variations are further CGMP violations since consistent, repeatable manufacturing is required.

Min Li:

Min Li was the Vice-President for ZHP Analytical Operations, and started with ZHP in September, 2014. Although his CV shows that he graduated from Johns Hopkins with a Ph.D in organic chemistry, he stated that he is not, "a process chemist." (Min Li 4/20/21 Dep. Tr., 12:7-11, 23:19-24:2, 33:22-24).

Min Li confirmed that while he was working for Merck, beginning in 2008 his "laboratory was very well-equipped with state-of-the-art analytical instruments including 9 mass spectrometers of different capabilities." (Min Li 4/20/21 Dep. Tr., 62:17-63:10). This is yet more confirmation that this technology was known and available in the scientific and pharmaceutical manufacturing fields throughout the relevant time period.

Dr. Li confirmed that he established CEMAT, which was wholly owned by ZHP and located in the ZHP Xunqiao site, to improve ZHP's capabilities in the identification of impurities in API and finished dose, and he confirmed that the identification of impurities is "part of the CGMP requirements." (Min Li 4/20/21 Dep. Tr., 72:7-74:6).

He discussed a powerpoint that described the "Mission of CEMAT…To solve the most challenging technical problems encountered from research and development to scale up and manufacture of drug substances and finished products, particularly those related to process impurities, degradation products, and solid state and polymorphism." He confirmed that "Process impurities would include, for example, the NDMA created by the zinc chloride process…And the creation of NDMA and NDEA in the TEA process with sodium nitrite quenching…". (Min Li 4/20/21 Dep. Tr., 74:17-76:10). He also confirmed the root causes of the impurities, including the manufacturing processes and cross-contamination. (Min Li 4/20/21 Dep. Tr., 76:14-79:22).

Dr. Li stated that ZHP did not have any information prior to June 2018 "indicating that any of the valsartan manufacturing processes could cause any nitrosamine to be created." (Min Li 4/20/21 Dep. Tr., 80:17-21). However, he then testified to the contents of a July 27, 2017 email sent to him and others within ZHP by Jinsheng Lin, who worked at CEMAT, indicating that it was known at that time that ZHP's valsartan API contained NDMA, which occurred due to the quenching with sodium nitrite, and that this was a "common problem in the production and

synthesis of sartan APIs." The email also confirmed the presence of nitrosamines would create "an extremely high GMP risk." (Min Li 4/20/21 Dep. Tr., 82:11-83:7, 85:7-86:2, 86:6-14, 87:19-88:7, 88:13-90:2, 90:7-10, 90:14-23). He also agreed that when the problem with the manufacturing process was learned by people outside the company, "that was a significant GMP problem…" (Min Li 4/20/21 Dep. Tr., 92:6-20).

Dr. Li testified with regard to a series of emails between Novartis and ZHP beginning May 22, 2018, in which Novartis asked ZHP to identify the source of various peaks seen on chromatography performed on valsartan API provided by ZHP to Novartis. On June 5, 2018, Novartis communicated its preliminary assessment that these peaks indicated the presence of NDMA. He was unaware of anyone at ZHP disclosing ZHP's prior knowledge going back at least to July, 2017, to Novartis. (Min Li 4/20/21 Dep. Tr., 198:13-204:2). He also identified the report from Solvias, the third-party laboratory hired by Novartis to test the API, and confirmed that the GC-MS technology used by Solvias to identify the NDMA had been available for a long time, including as of 2011 when the "processes were being developed," and ZHP purchased that technology at least as of 2013. (Min Li 4/20/21 Dep. Tr., 204:3-206:13). He also confirmed the location on chromatograms of the peak attributable to the NDMA, which was the subject of the July 27, 2017 email. (Min Li 4/20/21 Dep. Tr., 209:8-217:10). Dr. Li ultimately agreed that "the technology and the methodology was clearly available to identify the NDMA," as long as you "know what to look for" based on a risk assessment – which he confirmed is an ongoing process for the lifecycle of the drug. (Min Li 4/20/21 Dep. Tr., 230:9-19, 233:10-18).

Dr. Li testified with regard to the November 29, 2018 FDA Warning Letter that followed from the inspections on July 23, 2018 and August 3, 2018. Deviation 1 in the Warning Letter was "Failure of your quality unit to ensure that quality related complaints are investigated and resolved." This included "inadequate investigation of unknown peaks observed in chromatograms." (Min Li 4/20/21 Dep. Tr., 246:13-248:14). In this context, Dr. Li confirmed a stream of complaints from customers beginning in 2014 with regard to unknown peaks on chromatography, and despite ZHP's responsibility for the quality of the API, Novartis and the third-party lab it retained identified the NDMA in ZHP's valsartan API before ZHP advised Novartis of the source of the unknown peak. In addition, in this context Dr. Li again acknowledged that the NDMA in the valsartan API was documented in Dr. Lin's July 27, 2017 email. (Min Li 4/20/21 Dep. Tr., 261:17-269:20).

In the context of the November 28, 2018 FDA Warning Letter, Dr. Li confirmed that the FDA disagreed with ZHP's position that it could not have been expected to foresee or detect the NDMA due to a 'knowledge gap." With regard to the risk assessment, the FDA stated "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change." And the FDA stated further, "Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce." Finally, the

FDA confirmed, and Dr. Li agreed, that ZHP was "responsible for the quality of the drugs" produced by ZHP. (Min Li 4/21/21 Dep. Tr., 426:8-427:5, 430:11-434:10). In my opinion, ZHP was responsible for the quality of the valsartan API it produced with any and all manufacturing processes it utilized. Moreover, the scientific literature acknowledged by Dr. Li discussed the formation mechanism for the nitrosamines, and the availability of the mass spectrometry technology needed to identify the nitrosamines, before either manufacturing process was developed, and this is confirmed in Dr. Hecht's report.

Dr. Li was also questioned about the FDA's July 23, 2018 Establishment Inspection Report ('EIR"). He confirmed that cost was a factor in the development of the zinc chloride process, but that "the fundamental, you know, you know, you know, factor that need to be considered is, you know, the product produced by the new process need to be comparable with regard to the registered specifications." However, he acknowledged that the EIR documented that Jun Du told the FDA that, "the change control should have stated the purpose of the change was to save money. Mr. Du further stated the cost reduction was so significant it is what made it possible for the firm to dominate the world market share." (Min Li 4/21/21 Dep. Tr., 437:3-443:20).

Dr. Li confirmed that NDMA and NDEA were "drug-related impurities" as referenced in the FDA's 2008 Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, which states that "drug-related impurities presumably provide limited, if any, therapeutic benefits and because of their potential to cause cancer in humans, every feasible technical effort should be made to prevent the formation of genotoxic or carcinogenic compounds during drug substance synthesis or drug product manufacturing." (Min Li 4/21/21 Dep. Tr., 296:23-298:4). This is a fundamental ongoing, lifecyle requirement of CGMP that ZHP violated, extending from development through commercial marketing.

Dr. Li confirmed that every batch of valsartan manufactured with the zinc chloride process exceeded the FDA limit of 96 nanograms. (Min Li 4/21/21 Dep. Tr., 306:15-23). In this context, due to the "extremely high carcinogenic potency" of n-nitroso compounds including NDMA and NDEA the Guidance excluded those substances from the threshold approach. The European Medicines Agency Guidelines on the Limits of Genotoxic Impurities in effect from 2007 to 2018 similarly stated that due to "the potential to damage DNA at any level of exposure and that such damage may lead/contribute to tumour development. Thus for genotoxic carcinogens [including NDMA and NDEA] it is prudent to assume that there is no discernible threshold and that any level of exposure carries a risk." (Min Li 4/21/21 Dep. Tr. 308:14-309:2, 322:2-323:13, 329:3-13, 339:5-340:6).

Dr. Li also discussed the ICH guideline titled, "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – M7," dated February 6, 2013. This guideline repeats the fact that cohort of concern carcinogens, which, "may occur as impurities in pharmaceuticals," are to be excepted from the Threshold of Toxicological Concern approach, because they, "display extremely high carcinogenic potency. Acceptable intakes for these high-potency carcinogens would likely be significantly lower than

the acceptable intakes defined in this guideline." Dr. Li confirmed that per the ICH guideline the threshold approach would not apply to these substances. The guideline also indicates the importance of evaluating "potential degradation products." It also focuses on the importance of a risk assessment taking into account scientific knowledge, to identify and protect against potential degradation pathways. (Min Li 4/21/21 Dep. Tr. 381:1-390:20, 467:14-470:7). This was not done here by ZHP.

Dr. Li was shown a textbook, Purification of Laboratory Chemicals, published in 1996 through 2000, which reflected "scientific knowledge as of the late 1990s and 2000" that DMF could decompose at its boiling point to yield dimethylamine. (Min Li 4/21/21 Dep. Tr. 391:13-395:5). He was shown another scientific article published in 2009 titled "N.N-Dimethylformamide: much more than a solvent," also recognizing that DMF could decompose to produce dimethylamine, referencing a textbook published in 1966. (Min Li 4/21/21 Dep. Tr. 411:19-413:22).

He was also shown an article authored by a group from Beijing University of Technology published in 2010 in the Journal of Physical Chemistry titled "Theoretical Investigation of N-Nitrosdimethylamine Formation from Nitrosation of Triethylamine," including a discussion of the formation mechanism of NDMA from the reaction of dimethylamine and nitrous acid – exactly what occurred here with the zinc chloride process. (Min Li 4/21/21 Dep. Tr. 414:2-416:12). Notwithstanding these examples of what was known in the scientific literature, Dr. Li confirmed that due to a "knowledge gap" nobody at ZHP "considered the potential decomposition of the DMF to yield dimethylamine as part of the process." This included no indication that anybody at ZHP reviewed scientific literature on the subject, despite the requirement by the ICH guideline to do so. (Min Li 4/21/21 Dep. Tr. 408:13-24, 409:16-410:21).

Along the same lines, Dr. Li acknowledged that the May, 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, discussion on N-nitroso compounds, indicated that, "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA." He also confirmed that this reaction is what occurred in the zinc chloride process: "the zinc chloride process for the formation of NDMA, you know, was also under the acidic, you know, pH. So, yes, so from that perspective, yeah, they are consistent." He also confirmed that this is information "scientists would be aware of and have available to them" in 2011. Further, he acknowledged that it was known, as stated in the 1978 Monograph that, "The principal techniques employed for the analysis of volatile N-nitrosamines [including NDMA] have been described in a recent publication…The relative merits of high- and low-resolution mass spectrometry are discussed, since use of mass spectrometry as a confirmatory technique is particularly important." (Min Li 4/21/21 Dep. Tr. 458:13-465:11). Thus, Dr. Li confirmed that the reactions that caused the NDMA to form in the zinc chloride process, (known since 1865 per the Monograph) and the means to identify nitrosamines including the NDMA that formed, were well-known in the scientific literature, documented more than 30 years before the zinc chloride and TEA with sodium nitrite quenching processes were developed.

In this context, Dr. Li was shown and acknowledged that a draft of a Deviation Investigation Report within ZHP titled "Investigation Regarding an Unknown Impurity (Genotoxic Impurity)", indicated, "Due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied, and was unaware of the further reaction between degradation products and raw material." (Min Li 4/22/21 Dep. Tr. 528:5-531:4). This conclusion, which was not included in the final version of any Deviation Investigation Report by ZHP that I have seen, is consistent with my evaluation of the inadequate risk assessments performed by ZHP for the zinc chloride and TEA with sodium nitrite manufacturing processes.

Dr. Li confirmed that ZHP's testing, documented in ZHP's September 1, 2018 Response to DMF Information Request Letter, showed that all 783 batches tested and listed in the document exceeded the limit set by the FDA, ranging up to 627 times the limit for NDMA. (Min Li 4/21/21 Dep. Tr. 472:12-476:19).

Jucai Ge:

Jucai Ge is ZHP's Quality Assurance Director, API Division. (ZHP 322). Her recollection was that the first time an FDA inspector traveled to Chuannan to inspect the manufacturing facility occurred in 2007. " (Jucai Ge 4/27/2021 Dep. Tr. 19:5–11). ZHP had no specific department that was dedicated to professional translation of GMP documents from English into Chinese. (Jucai Ge 4/28/2021 Dep. Tr. 25:4–18). When FDA regulators would come to the Chuannan facility, Jucai Ge would use members of the sales staff to translate because there were no dedicated translators. (Jucai Ge 4/28/2021 Dep. Tr. 26:17–29:7). Jucai Ge testified that as the VP of Quality at Chuannan, it was her responsibility to improve operations and to make some quality improvements. (Jucai Ge 4/28/2021 Dep. Tr. 29:20–30:8). SMPs were applicable to all quality activities including manufacturing of APIs and finished drug formulations and relevant management in scope. (Jucai Ge 4/28/2021 Dep. Tr. 36:3–22). It was obviously important that the Director of Quality Assurance would be able to understand any controlling documents, including those only in the English language.

As of 2019, Jenson Ye, the Qualified Person (QP), managed the corporate quality assurance department. (Jucai Ge 4/28/2021 Dep. Tr. 37:15–20). In addition to the corporate quality department, the QP also managed the quality assurance departments at the various manufacturing facilities (such as Chuannan or Xunqiao). (Jucai Ge 4/28/2021 Dep. Tr. 37:21–38:13). As she was working on the "QA side," Ms. Ge did not work with the technical division, nor did she know what department was responsible for implementing ZHP's major API process change. (Jucai Ge 4/28/2021 Dep. Tr. 40:20–41:7). Ms. Ge could not answer whether the Quality Manual was limited in scope to just ZHP, or was extended to other companies owned by ZHP, such as Shanghai Syncores or Prinbury. (Jucai Ge 4/28/2021 Dep. Tr. 41:9–47:12).

At the time Novartis informed ZHP about the NDMA impurity, the Quality Control department of Chuannan did not have a GC-MS machine. (Jucai Ge 4/28/2021 Dep. Tr. 49:3–14).

Even though the Chuannan site was separated into east and west, these two entities were managed by one quality control and quality assurance department. (Jucai Ge 4/28/2021 Dep. Tr. 56:14–57:12). All SOPs and SMPs were kept in Chinese, and would only be translated if they were the types of documents that were requested during an audit. (Jucai Ge 4/28/2021 Dep. Tr. 61:14–62:2).

The change control system is a system that manages the initiation, evaluation, and approval of any change. (Jucai Ge 4/28/2021 Dep. Tr. 72:2–13). Ms. Ge could not understand a situation in which she, as QA director, would be involved in determining and evaluating whether a proposed change had an impact on product quality. (Jucai Ge 4/28/2021 Dep. Tr. 79:19–80:11). The QA department classified the November 2011 change to the zinc chloride process as a "critical change." (Jucai Ge 4/28/2021 Dep. Tr. 127:5–16).

QA was responsible for determining which other divisions of the company should be included in the assessment of a potential process change. (Jucai Ge 4/28/2021 Dep. Tr. 136:13–18). The QA department decided that the research department of ZHP did not need to review the proposed manufacturing change for the valsartan API because the product was already commercialized. (Jucai Ge 4/28/2021 Dep. Tr. 138:4–16). QA should "not be concerned about the cost" of a proposed change, but should rather be focused on the quality change. (Jucai Ge 4/28/2021 Dep. Tr. 144:18–145:9). QA has the ultimate authority to reject a process change. (Jucai Ge 4/28/2021 Dep. Tr. 150:3–151:19). When reviewing the process change, the technical division of the company decided that a cleaning validation of the impact of the potential change did not need to be conducted. (Jucai Ge 4/28/2021 Dep. Tr. 155:5–157:23; ZHP00000163).

Ms. Ge testified that with major deviations, it was sometimes not possible to find the root cause, using an analogy to a plane crash into the ocean: "like the tragedy of the Malaysian airlines as an example." (Jucai Ge 4/28/2021 Dep. Tr. 169:22–170:18).

Ms. Ge could not testify about the existence of a quality agreement between ZHP and Shanghai Syncores existing prior to 2018. (Jucai Ge 4/29/2021 Dep. Tr. 203:4–208:14).

Ms. Ge testified that QA did not approve the proposed manufacturing change for the Irbesartan discussed in the July 27, 2017 email. (Jucai Ge 4/29/2021 Dep. Tr. 262:6–263:16). She testified that ZHP was not obligated to report any potential impurities to the FDA without any data. (Jucai Ge 4/29/2021 Dep. Tr. 283:7–9). In my opinion, the fact that NDMA was known to be present in valsartan and other sartans utilizing sodium nitrite quenching was, as Dr. Lin stated in the email, a significant CGMP issue. The failure to take immediate and definitive action in response to this knowledge and instead continuing to use the processes implicated by this knowledge, was a serious violation of CGMPs.

Ms. Ge confirmed that the technology to identify NDMA was available prior to June 2018, “Had we known prior to June 2018 that there was an impurity called NDMA, I believe my company would have been capable of developing such an analytical method for this impurity, just like what we did when we became aware of such an impurity in June 2018. (Jucai Ge

5/26/22 Dep. Tr. 119:7-120:21). Ms. Ge was one of the people who received the July 27, 2017 email.

Ms. Ge confirmed that when the FDA informed ZHP that its Valsartan was adulterated, "That means that in our manufacturing process, our methods, facilities, and controls did not conform to cGMP." (Jucai Ge 5/26/22 Dep. Tr. 26:10-29:5).

Qiangming Li:

Qiangming Li is the Senior Director of the Chuannan QC Department. (ZHP 255). He confirmed that ZHP received a series of customer complaints regarding unknown, or aberrant peaks on chromatography for valsartan API, some of which were focused on the area surrounding toluene. These included:

1. Ranbaxy/SunPharma on September 30, 2014 (Qiangming Li 4/14/2021 Dep. Tr. 130:7-170:11; ZHP01748896 (ZHP 260)).

2. Shanghai Pharmtech on November 20, 2014 (Qiangming Li 4/14/2021 Dep. Tr. 177:22-199:20; ZHP01748905 (ZHP 264)).

3. SunPharma on November 17, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 290:16-318:10; ZHP00405069 (ZHP 277); ZHP01313866 (ZHP 278)).

4. Vertex on December 21, 2016 (Qiangming Li 4/14/2021 Dep. Tr. 204:11-214:17; ZHP02630924 (ZHP 265); ZHP02630926 (ZHP 266).

5. Glenmark on December 29, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 254:22-290:4; ZHP00496153 (ZHP 271); ZHP00496155 (ZHP 272); ZHP02118712 (ZHP 273)).

6. Aurobindo on August 23, 2017 (Qiangming Li 4/15/2021 Dep. Tr. 343:21-372:9; ZHP02094739 (ZHP 281)).

7. Novartis on May 22, 2018 (Qiangming Li 4/15/2021 Dep. Tr. 386:17-466:17; ZHP00405021 (ZHP 284)).

Mr. Li confirmed that "NDMA elutes near the toluene peak in the residual solvent gas chromatography of ZHP's valsartan API" and that ZHP never used GC-MS to test valsartan API prior to June 2018. ((Qiangming Li 4/14/2021 Dep. Tr. 168:11-17; Qiangming Li 4/13/2021 Dep. Tr. 77:4-6). He explained that "[f]or the identification of the impurities, first we need to have the knowledge of the existence as well as the structure of such an impurity." (Qiangming Li 4/13/2021 Dep. Tr. 78:10-14). As established by Dr. Hecht, Dr. Najafi, and the testimony of other witnesses listed above, the potential creation of these impurities was known in the scientific community, and the technology to test for them was readily available.

Hai Wang:

Hai Wang is the President of Solco Healthcare (ZHP's United States distributor of finished dose pills), Senior Vice President of Prinston Pharmaceutical Inc., and Senior Vice President of Huahai US, Inc., and directly reports to Jun Du. (Hai Wang 3/10/21 Dep. Tr. 31:16-33:1, 34:7-12).

According to the Prinston website, the products sold by Prinston, "are manufactured in state-of-the-art GMP facilities using the highest quality assurance standards that meet the FDA regulatory requirements." (Hai Wang 3/10/21 Dep. Tr. 37:3-11). Solco made the same or similar representations to its customers. (Hai Wang 3/10/21 Dep. Tr. 44:12-45:6).

Mr. Wang confirmed that at all times Prinston and Solco represented that the valsartan "met appropriate standards reviewed and approved by the FDA. Since the product had the USP designations, or the USP specification, the requirement has been met. (Hai Wang 3/10/21 Dep. Tr. 62:18-63:18). In addition, Prinston and Solco always represented that the valsartan was Orange Book AB rated, meaning "it's the therapeutic equivalent of the brand name product…it has the same quality and purity as the brand name product…the drug was manufactured in compliance with current good manufacturing practice regulations." (Hai Wang 3/10/21 Dep. Tr. 82:4-85:10, 89:7-16). As set forth herein, these representations were not accurate.

Mr. Wang stated that all of the valsartan sold by Prinston and Solco in the United States contained NDMA, and confirmed that the FDA was advised that "NDMA is present at a level greater than 0. 5 ppm in all Huahai's drug substance batches for DMF 023491". (Hai Wang 3/10/21 Dep. Tr. 93:10-16, 154:3-16).

He confirmed that "the first valsartan pills manufactured by ZHP and sold in the United States, the first time they were received was October 2, 2015." Also, "even though ZHP owns Prinston and Solco, they still go through the formality of an official purchase order…They're two separate business entities." (Hai Wang 3/10/21 Dep. Tr. 96:8-97:8).

Mr. Wang explained that ZHP established that the NDMA levels in the API were assumed to carry over to the levels in the finished dose because this was a process related impurity, "not a result of degradation of the product" and this information was provided by Prinston to the FDA. (Hai Wang 3/10/21 Dep. Tr. 116:22-118:23, 144:15-147:1, 152:8-12, 158:8-159:6).

With regard to the DMF, he stated that the DMF holder was ZHP and its US agent was Huahai or Prinston. (Hai Wang 3/10/21 Dep. Tr. 134:11-21). Huahai, US was the US agent per documents provided. (*See, e.g.*, ZHP00079956; PRINSTON00012473).

Mr. Wang stated that Prinston did not ever test the finished dose because that was the responsibility of ZHP as the finished dose manufacturer per the terms of the quality agreement, and he also stated that Prinston did audit the ZHP manufacturing processes. (Hai Wang 3/10/21 Dep. Tr. 152:8-153:16). However, he testified that the manufacturing process utilized by ZHP to

manufacture the valsartan was of no interest to Prinston and Solco. (Hai Wang 3/10/21 Dep. Tr. 166:9-170:11).

Mr. Wang identified the quality agreement dated January 2016 between Prinston and ZHP, which stated, "The purpose of the Quality Agreement is to ensure that the roles and responsibilities are clearly defined with respect to relevant CGMPs, and Applicable Laws." He agreed that "both ZHP and Prinston had roles and responsibilities with respect to the current good manufacturing practices." It also identified the sources of applicable CGMPs including FDA regulations in 21 CFR parts 210 and 211, FDA regulatory inspection guides, and FDA guidances for industry. (Hai Wang 3/10/21 Dep. Tr. 171:3-7, 172:1-177:1, 181:8-182:2). "The purpose of the quality agreement, to ensure the products sold and distributed in the US meeting the applicable laws and the CGMP requirement." (Hai Wang 3/10/21 Dep. Tr. 178:4-24). Per the quality agreement, Prinston was required to implement quality standards including "an official compilation of specifications, analytical methods, and standardized assays used to insure the identity, strength, quantity, and purity of Product and API." (Hai Wang 3/10/21 Dep. Tr. 182:6-24).

Prinston provided information to the FDA in connection with the recall notice which included the ANDA numbers of A204821 for valsartan and A206083 for valsartan/HCTZ, and the beginning and ending manufacturing dates of May 2015 to March 2018, and that Prinston first marketed valsartan on June 9, 2015 and valsartan-HCTZ on February 9, 2016. Mr. Wang discussed the information provided in detail, including the statement of the root cause. (Hai Wang 3/10/21 Dep. Tr. 205:28-266:14). The recall notice confirmed that the NDMA caused "an unacceptable carcinogenic risk to the intended patient population." (Hai Wang 3/10/21 Dep. Tr. 274:19-283:19).

Mr. Wang confirmed that "No wants to have NDMA," in valsartan. (Hai Wang 3/10/21 Dep. Tr. 325:18-326:1).

Per the Quality Agreement, which was originally agreed to in 2011 and then revised in small part in 2016, and covered valsartan among other drugs, responsibilities were allocated between Prinston and ZHP, as follows (Hai Wang 3/10/21 Dep. Tr. 184:19-185:13,195:5-12; Hai Wang 3/11/21 Dep. Tr. 548:11-558:19):

Per 2.1.1, ZHP was responsible to "maintain adequate and qualified manufacturing and Quality Unit personnel in the Facility during the Manufacture of Product to ensure both compliance with CGMPs and the consistent manufacture of Product."

Per 2.2.2, ZHP was responsible to "maintain and operate the Facility utilized to manufacture Product in compliance with the CGMPs."

Per 2.4.1, ZHP was responsible to "Manufacture the Product in accordance with CGMPs, the Master Batch Records, Standard Operating Procedures, Specifications, Market Authorizations and All Applicable Laws."

Per 2.4.2, both ZHP and Prinston were responsible to "validate the process for Manufacturing the Product in accordance with CGMPs, Applicable Laws, Standard Operating Procedures to ensure that the Product consistently meets all requirements of the Market Authorizations."

Per 2.4.4, both ZHP and Prinston were responsible to ensure "Senior management, Quality Assurance, will review and approve process validation Protocols and final reports."

Per 3.3.2, in connection with Process Change Control, ZHP was responsible to "provide Prinston with all information required for evaluating the proposed changes, and, if necessary, to obtain amended market authorizations."

Per 3.3.3, in connection with Process Change Control, ZHP and Prinston were responsible to "provide the other party with written approval or rejection of proposed changes using the change request using the Change Request and Approval Form in Attachment C. Such approval shall not be unreasonably withheld."

Per 6.7.1, in connection with Market Actions, ZHP was responsible to "notify Prinston as soon as reasonably possible but no later than one business day of any information of which it is aware related to the Manufacturing of the Product which may affect the safety or the continued marketing of the Product."

Per 7.1, ZHP was required to "allow and support one quality audit by Prinston per calendar year per Facility," and per 7.1.6 ZHP was required to respond in writing within 30 days of receiving Prinston's "written report on audit observations and conclusions." Per 7.1.7 there was a requirement that "Prinston and ZHP will discuss and agree on a CAPA to address the audit observations and conclusions."

Mr. Wang also confirmed that the report of the audit conducted by Prinston in March, 2014 listed the following deviations and criticisms (Hai Wang 3/11/21 Dep. Tr. 559:4-567:5):

1. Poor quality reviews.
2. The supplier qualification program is unreliable.
3. Lack of Understanding of CGMP implementations.
4. Weak method validation.
5. Lack of evidence for obtaining reliable results.
6. Poor review for manufacturing data.
7. Lack of using system approach for CAPA implementation.
8. Poor quality assurance review.

Out of specification results are investigated and "if no assignable cause is found a process is filed and it's discussed there, and this was deemed "major misinterpretation to the FDA guideline of the out of specification testing."

The quality of documentation is deficient.

Change control documentation is deficient.

"[B]atch records included some monitoring data during the manufacturing of API that looked untrue. It is neither real time nor actual data. Such practice usually receives severe response from any agency if discovered during inspections. Therefore, senior management must pay the utmost attention to take the necessary steps to rectify it once and for all."

"Please be advised that quality system deficiencies regarding Xunqiao site are very similar to Chuannan site…". This series of deficiencies was significant, and per the quality agreement if these issues were not confirmed to be remedied Prinston was supposed to cease the use of API manufactured in the facilities with audited CGMP deficiencies. I have not seen confirmation that all of these issues were followed up on and remedied and we know that significant ongoing deviations existed in connection with the manufacture of the Valsartan API and finished dose at these facilities.

In connection with the change notification to Prinston for the zinc chloride process, Mr. Wang confirmed that ZHP notified Prinston that there was "no adverse change in qualitative and quantitative impurity profile." He also confirmed that ZHP would have to have data to support that representation. However, he did confirm that both ZHP and Prinston had responsibilities to review the changes, and ensure "all the changes will meet the CGMP requirement." Hai Wang 3/11/21 Dep. Tr. 569:3-577:16)

Jun Du:

Jun Du identified himself as the Vice Chairman of the Board of Directors of ZHP, and stated that he also held the title of Executive Vice President of ZHP on an interim basis, to attend audits by the FDA or European Union or EHS, when Baohua Chen was unavailable, in order to coordinate with the regulatory agency performing the audit, including in July and August, 2018. (Jun Du 5/27/21 Dep. Tr. 25:13-34:24). A ZHP powerpoint identifies Mr. Du as a GMP expert though he qualified that as referring to his founding of an engineering firm and in that capacity designing a drug manufacturing facility and production lines and confirming their compliance with GMP requirements." (Jun Du 5/27/21 Dep. Tr. 54:16-56:14).

Mr. Du identified himself as the CEO of Prinston Pharmaceuticals and CEO of Solco Healthcare. Prinston "engages in the finished dose products, research and development, as well as the regulatory affairs of such products. It owns an ANDA of generic drugs. It also owns a sales company and manufacturing facility or facilities," and is the 100 percent owner or Solco, and Solco was described as "a company that sells the generic drugs of Prinston for which Prinston holds the ANDA. He also stated that he is the CEO of Huahai, U.S. and identified Huahai, U.S. as a wholly owned subsidiary of ZHP, and owner of the majority of stock of Prinston, and that "ZHP sells their API products directly in the U.S. market through Huahai U.S., including both the

research and development APIs, as well as commercialized APIs." (Jun Du 5/27/21 Dep. Tr. 40:1-44:11, 49:3-9, 54:7-21).

Mr. Du testified with regard to the quality agreement between ZHP and Prinston, and confirmed that "The finished dose facility of ZHP was supposed to make sure that their API would comply with the requirements of the GMP." (Jun Du 5/27/21 Dep. Tr. 90:6-21). Mr. Du also confirmed that Section 6.7.1 of the quality agreement required ZHP to "notify Prinston as soon as reasonably practicable but no later than one business day of any information of which it is aware related to the manufacturing of the product which may affect the safety or the continued marketing of the product," and stated this referred to the finished dose products sold by ZHP to Prinston. (Jun Du 5/27/21 Dep. Tr. 97:9-99:15).

Mr. Du was questioned about the July 27, 2017 email from Jinsheng Lin, which he stated he had never seen until it was shown to him one week before his deposition. He did confirm that CEMAT, where Jinsheng Lin was employed conducted quality research including analytical methods into impurities, and identified most of the recipients of the email. (Jun Du 5/27/21 Dep. Tr. 101:8-18, 102:4-107:5). Mr. Du confirmed the substance of the letter, including that the impurity seen in the irbesartan was likely an N-NO compound, and that, "it was similar to the NDMA from the sodium nitrite quenching in valsartan." (Jun Du 5/27/21 Dep. Tr. 107:12-115:23). Mr. Du was also shown a powerpoint regarding CEMAT and the role of Dr. Jinsheng Lin, including that he was in charge of the "lab for process and degradation impurity research," which was responsible "to systematically design and conduct forced degradation research on drugs to research the mechanism of process impurity formation, to study the degradation pathway of the degradation impurities…" and that the NDMA and NDEA impurities in the valsartan at issue were process impurities. (Jun Du 5/27/21 Dep. Tr. 116:11-120:5).

Mr. Du also discussed the November 5, 2018 Deviation Investigation Report with regard to the triethylamine process. ("DIR"), including identification of the same root cause as identified in the July 27, 2017 email. (Jun Du 5/27/21 Dep. Tr. 124:3-134:8). Mr. Du confirmed that "From the GMP perspective, if it is confirmed that NDMA is discovered in valsartan, then an investigation should be immediately started just as Jucai Ge did in June of 2018 by initiating a deviation investigation." (Jun Du 5/27/21 Dep. Tr. 148:1-14). In my opinion that was required as of July 27, 2017, or whatever date the NDMA was discovered in the valsartan, based on the content of that email. ZHP's failure to do so, or to notify the FDA or its customers, until after Novartis pushed it to do so in June, 2018, was a violation of GMPs.

Mr. Du confirmed that both Prinston and Solco issued press releases announcing the recall of the valsartan containing the NDMA impurity, and that the press releases stated in part that the recall was due to "an unacceptable carcinogenic risk to the intended patient population." (Jun Du 5/27/21 Dep. Tr. 91:17-94:22). I agree with that assessment of the risk of NDMA and NDEA in the valsartan.

Mr. Du signed ZHP's August 26, 2018 response to the FDA 483 observations from the July 23, 2018 to August 3, 2018 inspection, in his capacity as Executive Vice President of ZHP. (Jun Du

5/27/21 Dep. Tr. 57:19-60:10). The letter states that ZHP moved promptly to notify the regulatory authorities and its customers, and other steps taken, once the NDMA was discovered. (Jun Du 5/27/21 Dep. Tr. 60:11-70:23). This appears to conflict with the July 27, 2017 email sent by Jinsheng Lin, Ph.D. and the testimony of Min Li, regarding knowledge within ZHP that there was NDMA in its valsartan, and the root cause for that impurity.

Mr. Du confirmed that the letter correctly set forth the root cause of the NDMA formed during the zinc chloride process: 'the ultimate reason for the presence of NDMA in valsartan API is due to this process change in which the solvent dimethylformamide (DMF) was introduced and its impurity/degradant dimethylamine, unexpectedly reacts with nitrous acid (generated in situ between sodium nitrite and hydrochloric acid) during the subsequent quenching step in the presence of the product of that step." (Jun Du 5/28/21 Dep. Tr. 227:12-229:8).

The August 26, 2018 letter also included ZHP's primary explanation for its inadequate risk assessment and failure to identify the nitrosamine contamination when the zinc chloride process was being developed, including that, "it is not the residual DMF that reacts with nitrous acid of the next step, but rather it is the trace amount of dimethylamine, an impurity/degradant of DMF that reacts with nitrous acid to form NDMA, which adds a further dimension over the current thinking, logic and strategy for the evaluation of potential genotoxic impurities. It is this extra dimension over the current industry practice that obscured us from foreseeing this impurity during the process change from triethylamine process to zinc chloride process." (Jun Du 5/28/21 Dep. Tr. 232:18-234:6).

Mr. Du was asked about the FDA's November 29, 2018 Warning Letter written in response to the August 26, 2018 letter written by Mr. Du, which stated in part: "This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API)," including, "Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API," which Mr. Du confirmed, "was the zinc chloride process change for valsartan." The letter also stated, "Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 351 (a)(2)(B)." (Jun Du 5/28/21 Dep. Tr. 234:13-237:16). Mr. Du also confirmed that the Warning Letter was even more specific about the CGMP violations, including, "you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine," and, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." Mr. Du agreed that it was most important for ZHP to ensure the safety of patients. (Jun Du 5/28/21 Dep. Tr. 237:18-243:20).

Mr. Du claimed in the course of this testimony that the zinc chloride process change was "approved by the FDA," which is repeated multiple times. However, the process change was documented and filed with the FDA in a DMF amendment, which is not "approved" when it is filed, rather at most it is reviewed for completeness and filed for future reference in an ANDA. As described above, the DMF for the zinc chloride process stated unequivocally that there were no genotoxic impurities resulting from the process, and neither the DMF nor the ANDAs for valsartan manufactured with the zinc chloride process or TEA with sodium nitrite quenching process disclosed the presence of NDMA. The FDA ultimately approved ANDAs referencing the DMF, approving the manufacture and sale of the drug formulation and impurity profile described, which did not include the genotoxic, mutagenic, probable human carcinogens (as described by ZHP and Prinston in their own documents) NDMA or NDEA.

Mr. Du also referred to the adulteration language in the FDA Warning Letter as "their uniform statement in the warning letter," however the finding of adulteration by the FDA was quite significant, and not a mere matter of form or boilerplate language. The CGMP violations specific to the ongoing, repeated inadequate risk assessments and failures to appropriately test for NDMA or NDEA, leading to the sale of valsartan containing NDMA and NDEA, resulted in the API being adulterated by definition.

The Warning Letter directly addressed and rejected ZHP's position in the August 26, 2018 letter that it could not have been expected to identify the nitrosamine impurities, stating, "Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce." Mr. Du agreed that ZHP was responsible for the quality of the drugs produced by ZHP. (Jun Du 5/28/21 Dep. Tr. 247:17-250:22).

In this connection, Mr. Du was shown a draft of the deviation investigation report, which stated, "Due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied, and was unaware of the further reaction between degradation products and raw material." Mr. Du focused on the fact that the document was a draft. (Jun Du 5/28/21 Dep. Tr. 270:14-272:3). This explanation for what occurred, which was removed before the Deviation Investigation Report was finalized, was accurate, since as admitted by ZHP in the Stipulation, no scientific research was undertaken with regard to the potential degradation products of DMF or the potential resulting chemical reactions, and multiple ZHP witnesses agreed that what occurred was described in scientific literature pre-dating the development of the manufacturing processes that led to the formation of NDMA and NDEA. As stated in multiple places in this report, ZHP failed to conduct an adequate risk assessment, in particular its lack of research and understanding of the chemical reactions it was putting in motion from the outset, and then on an ongoing basis throughout the lifecycle of the drug product.

Mr. Du confirmed that the FDA placed ZHP on Import Alert on September 28, 2018, and that, "This import ban stopped the manufacturing of API products at our Chuannan facility. Not limited to valsartan. That's a decision made by the FDA." (Jun Du 5/28/21 Dep. Tr. 251:2-15).

Mr. Du was also questioned about the FDA Establishment Inspection Report for the July 23, 2018-August 3, 2018 inspection, which quoted Mr. Du's explanation for the change to the zinc chloride process as, "Mr. Jun Du, executive vice president, apologized and stated the change control should have stated the purpose of the change was to save money. Mr. Du further stated the cost reduction was so significant it is what made it possible for the firm to dominate the world market share." Mr. Du denied that he made that statement to the FDA investigator. (Jun Du 5/28/21 Dep. Tr. 230:6-232:7).

Minli Zhang:

Minli Zhang is ZHP's Deputy Director of Non-Sterile Formulation Preparations Manufacturing. (ZHP 162). The Chuannan and Xunqiao sites were about an hour away from one another by car. (Minli Zhang 3/22/2021 Dep. Tr. 35:18–23). She explained that Jenson Ye, QP for the company, was responsible for both the Xunqiao and Chuannan manufacturing facilities. (Minli Zhang 3/22/2021 Dep. Tr. 37:1–21). As the QA for Xunqiao, Zhang was responsible for quality testing and in-process research. (Minli Zhang 3/22/2021 Dep. Tr. 41:23–43:9). GMP required QA to be separate from the manufacturing and distribution units. (Minli Zhang 3/22/2021 Dep. Tr. 49:11–50:1). All of the SMPs and SOPs can either be categorized as a management document, a department document or a specific operations or processes document. (Minli Zhang 3/22/2021 Dep. Tr. 66:15–67:6).

Quality is meant to be "assessed from an impartial standpoint." (Minli Zhang 3/22/2021 Dep. Tr. 80:10–21). QA and QC were responsible for preparing the standards at Xunqiao related to the assessment of the valsartan API. (Minli Zhang 3/22/2021 Dep. Tr. 92:3–13). The QA department at Xunqiao would not review the Chuannan deviation reports because Chuannan was treated like a supplier. (Minli Zhang 3/22/2021 Dep. Tr. 99:14–23).

Ms. Zhang's English skills were limited so she could only understand the simple words in the Prinston and ZHP quality agreement such as ""quality agreement"" and "Zhejiang Huahai Pharmaceutical Co." (Minli Zhang 3/23/2021 Dep. Tr. 121:1–122:8). The Prinston and ZHP Quality Agreement was only written in English, so if Zhang needed to read the agreement, she would need to have her colleagues translate the terms to her. (Minli Zhang 3/23/2021 Dep. Tr. 123:2–16).

ZHP was required to give Prinston process changes, specification changes, and deviation reports. (Minli Zhang 3/23/2021 Dep. Tr. 133:14–134:14). Prinston was required to approve any process changes prior to their implementation. (Minli Zhang 3/23/2021 Dep. Tr. 136:20–137:14). Prinston was the one who ultimately decided whether a process change necessitated the filing of a new regulatory submission. (Minli Zhang 3/23/2021 Dep. Tr. 140:9–141:6).

Ms. Zhang did not view the employees at Prinston as colleagues, but rather viewed them as clients. (Minli Zhang 3/23/2021 Dep. Tr. 146:24–147:7). Ms. Zhang would only give further documentation to support process changes to certain employees at Prinston. (Minli Zhang 3/23/2021 Dep. Tr. 148:16–149:15).

If the API manufacturing process change included a change to the key synthesis steps, it would necessitate re-validating the manufacturing process. (Minli Zhang 3/23/2021 Dep. Tr. 170:15–23). If a key solvent had been changed in the API manufacturing process, the process would need to be re-validated. (Minli Zhang 3/23/2021 Dep. Tr. 171:2–12). She testified that one should use a tool like a fishbone chart (it is technically a diagram) to assess every aspect of potential risk associated with pharmaceutical manufacturing. (Minli Zhang 3/23/2021 Dep. Tr. 190:8–23).

Prinbury was responsible for developing the analytical methods used to analyze valsartan and they were also assisting in the manufacturing of ANDA submission batches. (Minli Zhang 3/23/2021 Dep. Tr. 200:9–19). Ms. Zhang couldn't say for sure whether there was a quality agreement in place between ZHP and Prinbury related to the development of Valsartan finished dose manufacturing. (Minli Zhang 3/23/2021 Dep. Tr. 213:17–214:7).

Xunqiao would qualify all API suppliers and would renew this qualification for every product they purchased from that API supplier. (Minli Zhang 3/24/2021 Dep. Tr. 254:9–255:2). Ms. Zhang did not know whether Chuannan was re-validated again prior to commercialization of the valsartan finished dose product. (Minli Zhang 3/24/2021 Dep. Tr. 263:21–264:17). Zhang was not sure whether Chuannan ever submitted a supplier questionnaire to Xunqiao QA as part of a supplier qualification. (Minli Zhang 3/24/2021 Dep. Tr. 266:22–268:14).

The SOP for API Release at Xunqiao provided that any API received from Chuannan was to be tested according to internal standards, whereas material received from “external” vendors was not. (Minli Zhang 3/24/2021 Dep. Tr. 304:11–306:23). The SOP for API release testing had no provisions related to renewed changes, but instead would "fall into the change management procedure which is under the Supply Management Procedure." (Minli Zhang 3/24/2021 Dep. Tr. 307:15–308:17).

Xunqiao never conducted their own residual solvent testing of the valsartan API manufactured at Chuannan, and instead only relied on the testing conducted at Chuannan. (Minli Zhang 3/24/2021 Dep. Tr. 316:12–317:24).

Periodically Xunqiao would engage in a practice where they would begin shipping finished dose product to the United States prior to release, and would include something called a "Certificate of Analysis "only for shipping." (Minli Zhang 3/24/2021 Dep. Tr. 339:1–341:22). Prinston always retained the ability to request additional testing that would need to be required for the release of API prior to the manufacture of the finished dose of the product. (Minli Zhang 3/25/2021 Dep. Tr. 370:2–21). When there was an API manufacturing change, Chuannan would

convey this change directly to Prinston. Prinston would then notify Xunqiao of the change, who would then initiate corresponding changes to the release specification to "decide whether to release or not." (Minli Zhang 3/25/2021 Dep. Tr. 377:15–378:2).

Xunqiao only conducted identification testing, and for the rest of the "release" process, Xunqiao would "resort to the test provided by Chuannan to see if their test results would meet" Xunqiao's quality standard requirements. (Minli Zhang 3/25/2021 Dep. Tr. 384:4–385:3).

When conducting a deviation investigation, Xunqiao QA would not review the batch records associated with the manufacture of Valsartan API unless the root cause was determined to be the API. (Minli Zhang 3/25/2021 Dep. Tr. 459:6–23). At the time Zhang was notified about the discovery of NDMA, Xunqiao did not know "whether NDMA was a serious impurity or not." (Minli Zhang 3/26/2021 Dep. Tr. 491:9–24). Xunqiao QA did not notify Prinston about the impurity, nor were they present in any meeting with Prinston about the impurity. (Minli Zhang 3/26/2021 Dep. Tr. 493:2–495:14).

Upon receipt of notification about the NDMA impurity, Xunqiao continued to manufacture any Valsartan that was in process until packaging, and then quarantined the product in the packaging. (Minli Zhang 3/26/2021 Dep. Tr. 499:2–20).

The only labs which were contracted to conduct NDMA testing on the Valsartan finished dose were the Advanced Analytical Center and Prinbury. (Minli Zhang 3/26/2021 Dep. Tr. 555:10–23).

After the finished dose products were shipped, the products became the responsibility of Prinston. (Minli Zhang 3/26/2021 Dep. Tr. 556:21–557:16).

Remonda Gergis:

Remonda Gergis is Prinston's Vice President of Quality Assurance. (ZHP 88). She testified that CGMP provides the guidance to conduct a "comprehensive approach " to enable a manufacturer to get to the "root cause " of an issue. " (Remonda Gergis 2/1/2021 Dep. Tr. 37:18–38:2). According to Ms. Gergis, API is the most important aspect of the drug product because it "is the part that ha[s] the pharmacological effect to the patient." (Remonda Gergis 2/1/2021 Dep. Tr. 46:8–12).

When she began working in 2009, Remonda Gergis was the only QA employee working for the company in the United States. (Remonda Gergis 2/1/2021 Dep. Tr. 61:13–18). When Ms. Gergis was interviewing for the job to head up the Quality Assurance department for the finished dose products, she did not speak to anyone in China, but does recall they did show her "very general" photos. (Remonda Gergis 2/1/2021 Dep. Tr. 62:16–63:19).

Despite working for a Chinese parent company, Remonda Gergis could neither speak nor read Chinese. (Remonda Gergis 2/1/2021 Dep. Tr. 75:2–9). Ms. Gergis described the QA

associates in China as a "young group of people." (Remonda Gergis 2/1/2021 Dep. Tr. 87:5–14). Ms. Gergis believed this "young" group of people "maybe didn't have the enough experience in terms of GMP." (Remonda Gergis 2/1/2021 Dep. Tr. 88:17–89:2).

Ms. Gergis testified that she initiated a Quality Agreement between Prinston and ZHP because she believed it was important to delineate the responsibilities between the parties. (Remonda Gergis 2/1/2021 Dep. Tr. 89:18–91:20). The first QA agreement between Prinston and ZHP was signed after Ms. Gergis's arrival in 2011. (Remonda Gergis 2/1/2021 Dep. Tr. 92:10–19). Quality agreements are considered an "industry practice." (Remonda Gergis 2/1/2021 Dep. Tr. 94:6–15).

The quality agreements between Prinston and ZHP were not specific to any particular product. The list of products that were subject to the QA were listed in an attachment appended to the back of the quality agreement. (Remonda Gergis 2/1/2021 Dep. Tr. 96:4–20). The ZHP facilities that manufactured the finished dose product were considered distinct entities from the ZHP facility that manufactured API because "they have their own...systems [and] have their own manufacturing area." (Remonda Gergis 2/1/2021 Dep. Tr. 100:3–19).

Prinston QA was allegedly responsible for compiling specifications for the finished dosage product. (Remonda Gergis 2/1/2021 Dep. Tr. 108:24–110:19). While Ms. Gergis testified that Prinston was responsible for developing specifications for the finished dosage products at their non GMP compliant lab, Ms. Gergis testified she could not recall any of the names "because they are all Chinese names." (Remonda Gergis 2/1/2021 Dep. Tr. 110:21–114:12).

This Prinston laboratory that developed the specifications for the finished dose did not conduct any testing on the API used in those finished dosage products. (Remonda Gergis 2/1/2021 Dep. Tr. 114:13–19). Prinston expected ZHP to follow the specifications they set forth for their finished drug products. (Remonda Gergis 2/1/2021 Dep. Tr. 115:13–116:6).

Ms. Gergis testified that Prinston's regulatory affairs division was responsible for ensuring that the master batch records for their finished dosage products complied with the market authorizations set forth for those products. (Remonda Gergis 2/1/2021 Dep. Tr. 118:8–119:5). However, Ms. Gergis then testified that she did not believe regulatory affairs reviewed the master batch records." (Remonda Gergis 2/1/2021 Dep. Tr. 119:22–120:2). Ms. Gergis testified that the reason that Prinston's regulatory department was to review master batch records against the FDA submissions was to "make sure there is no change in the process between what was submitted to the FDA and the ones that they will be using for the commercial product." (Remonda Gergis 2/1/2021 Dep. Tr. 120:3–121:3). Prinston's regulatory affairs department was also responsible for being aware of any changes made to the API manufacturing process. (Remonda Gergis 2/1/2021 Dep. Tr. 123:10–124:12).

As part of the quality agreement it was ZHP's responsibility to investigate and/or respond to any questions raised by the regulatory agency to the extent the question related to manufacturing issues. (Remonda Gergis 2/1/2021 Dep. Tr. 126:9–22). However, as the ANDA

holder, Prinston was responsible for the product. (Remonda Gergis 2/1/2021 Dep. Tr. 128:23–129:10).

As part of the quality agreement, Prinston would not conduct any independent validation of the processes, and would merely "review the validation results or the validation protocols and reports." (Remonda Gergis 2/1/2021 Dep. Tr. 130:9–23).

When there was a major change made to a manufacturing process, it was "necessary" to conduct a new validation protocol. (Remonda Gergis 2/1/2021 Dep. Tr. 139:1–140:3). Prinston bore no responsibility for conducting any validation protocols for the manufacture of API. (Remonda Gergis 2/1/2021 Dep. Tr. 142:23–143:20).

Despite being the QA director for Prinston, Ms. Gergis never worked with the QA director at the Chuannan API manufacturing facility, aside from conducting audits. (Remonda Gergis 2/1/2021 Dep. Tr. 144:8–22).

As the ANDA holder, Prinston had the responsibility for auditing the API manufacturer to make sure that the "operation is in compliance with GMP." (Remonda Gergis 2/1/2021 Dep. Tr. 147:12–148:1). Prinston was also responsible for qualifying suppliers, which meant that they would sometimes have to request API to make sure that it is "conforming with the specification of the API." (Remonda Gergis 2/1/2021 Dep. Tr. 148:3–19). However, Prinston did not conduct such testing, and instead believed that ZHP's finished dose manufacturer would somehow qualify the API manufacturer. (Remonda Gergis 2/1/2021 Dep. Tr. 148:21–149:17).

Prinston would audit its suppliers every two to three years. (Remonda Gergis 2/1/2021 Dep. Tr. 152:18–21). For significant changes, Ms. Gergis would expect a lot of documentation to be provided by ZHP. (Remonda Gergis 2/1/2021 Dep. Tr. 158:5–159:17).

Ms. Gergis testifed that because Prinston was the ANDA holder, it was important to receive notifications of process changes because "we need to know if there is anything - any changes to the product, we need to be aware of." (Remonda Gergis 2/1/2021 Dep. Tr. 159:19–160:4).

It was important to know all the details of the change because it would have an impact on whether they needed to ask the FDA for approval prior to the change and make other notifications to the FDA. (Remonda Gergis 2/1/2021 Dep. Tr. 160:14–161:14). While Ms. Gergis would extensively review change management for the finished dose manufacturing, and even though ZHP was required to provide notifications of changes to the FDA, she was not responsible for looking at changes to the API. (Remonda Gergis 2/1/2021 Dep. Tr. 161:15–163:3). Ms. Gergis testified it was Lijie Wang's responsibility to approve API manufacturing changes and make that evaluation. (Remonda Gergis 2/1/2021 Dep. Tr. 163:5–22).

Jenson Ye was the VP of Quality for both the finished dose and API manufacturing at ZHP. (Remonda Gergis 2/1/2021 Dep. Tr. 180:19–181:4). Because Ms. Gergis did not speak or read

Chinese, when she traveled to ZHP for audits, she would have to rely on employees there to translate any Chinese language documents for her. (Remonda Gergis 2/1/2021 Dep. Tr. 185:19–186:21."

While ZHP was required to notify Prinston of any adverse FDA audits/inspections and the observations, ZHP did not actually provide Ms. Gergis with the FDA's document, and instead summarized the audit themselves. (Remonda Gergis 2/1/2021 Dep. Tr. 212:19–215:12).

While Ms. Gergis could request the FDA's actual written reports documenting the inspection, she didn't request it as a matter of course. (Remonda Gergis 2/1/2021 Dep. Tr. 227:16–228:15).

Ms. Gergis testified that she was very upset over a deviation that occurred once because it wasn't even caught until the very end of the process. (Remonda Gergis 2/1/2021 Dep. Tr. 241:9–244:17). Ms. Gergis recalls getting a call in the middle of the night that the ZHP API site discovered an "unknown impurity in the chromatogram of valsartan." (Remonda Gergis 2/1/2021 Dep. Tr. 266:5–19). Ms. Gergis recalled John Iozzia being "kind of frustrated " because he didn't "have guidance from ZHP API in terms of how to respond to any customers." (Remonda Gergis 2/1/2021 Dep. Tr. 273:10–274:17). Ms. Gergis "wasn't too happy " with the way some aspects of the post-recall investigation were being conducted because an investigation report was just presented to her by ZHP "as everything is said and done." (Remonda 2/1/2021 Dep. Tr. 282:1–283:13).

FDA Investigation, 483's, Warning Letter, Establishment Inspection Report, Import Ban

Following ZHP's disclosure of the NDMA impurity to the FDA, the FDA initiated an investigation. On July 23-August 3, 2018 FDA performed a foreign comprehensive "For Cause" inspection of the API manufacturing site located at Chuannan, Linhai, Taizhour, Zhejiang.

Eleven (11) observations were cited on Form FDA 483, Inspectional Observations, date issued August 3, 2018. (ZHP00061069-79. In a letter from FDA to Mr. Du dated September 21, 2018, which enclosed the Form FDA 483, FDA stated the July 23-August 3, 2018 inspection resulted in an "Official Action Indicated" (OAI) inspection classification, and that the facility was "considered to be in an unacceptable state of compliance with regards to CGMP." (ZHP00061068). An OAI classification is the most severe classification assigned by FDA, citing regulatory and/or administrative actions will be recommended. Food & Drug Administration, *Inspections Database Frequently Asked Questions* (May 11, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions; Food and Drug Administration, *FMD 86: Establishment Inspection Report Conclusions and Decisions* (Jan. 28, 2014), https://www.fda.gov/media/87643/download. Administrative actions and enforcement activities can range from a Warning Letter, notifying the firm of a violation and requesting correction, to criminal prosecution of an individual or firm. Food & Drug

Administration, *Types of FDA Enforcement Actions* (July 14, 2022), https://www.fda.gov/animal-veterinary/resources-you/types-fda-enforcement-actions.

On September 28, 2018, FDA issued a letter to Mr. Du of ZHP, informing him that ZHP had been placed on the Import Alert list (Import Alert 66-40) and that future shipments were subject to refusal of admission to the United States until ZHP could demonstrate their products were in CGMP compliance. (ZHP00061080).

FDA issued a Warning Letter (320-19-04) to ZHP on November 29, 2018, notifying ZHP of significant deviations from CGMPs for their API manufacturing operations, and stating that the API was consequently adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 U.S.C. 351(a)(2)(B).

The eleven observations resulting from the inspection had been listed on the Form FDA 483. The observations are extensive, including for example, the first observation stated was: "The change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate, and:

a) you do not always conduct a formal risk assessment for critical changes to evaluate the potential impact of the proposed changes on the quality of intermediates or APIs…

a)i). you did not conduct and document a formal risk assessment for Change Request PCRC-11025…

a)ii) you hired an outside laboratory to conduct a small lab scale research project…you initiated validation on a commercial scale to change your validated manufacturing process without conducting pilot scale or other small scale batches…you initiated validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to your validated manufacturing process on the quality of intermediates and APIs…

b) you do not have an adequate change control system requiring scientific judgement to determine what additional testing and validation studies are appropriate to justify changes to a validated manufacturing process. You do not always have data to support approval of changes to validated processes.

c) you do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated procedure. You do not consistently classify changes…Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change. As described herein, The change request (PCRC-11025) closed November 29, 2011, designated the change to the zinc chloride manufacturing process as a "critical change" to the Valsartan manufacturing process to increase batch yields. As previously

discussed, this was a critical change to the process, that ultimately led to NDMA formation in the API. This was also a violation of CGMPs and risk assessment requirements, and in addition ignored the report from Shanghai Syncores indicating that pilot scale evaluation was required, following the lab scale evaluation performed by Syncores during development of the zinc chloride process. As set forth above, Mr. Gu testified that pilot scale was required by cGMPs. (Eric Gu 4/5/21 Dep. Tr., 39:13-45:3)

d) …Your quality unit does not always follow your written procedure for change control…

The Warning Letter also stated that there was no evidence of a documented compliant risk assessment to evaluate the impact of the proposed change to the identity, strength, quality, purity or potency of the API as required in various sections of GCMPs (21 CFR 211) and ICH Q7, Good Manufacturing Practices for Active Pharmaceutical Ingredients (APIs). As described herein, we know that ZHP failed to evaluate the potential chemical reactions that caused the NDMA contamination, and failed to test for potential nitrosamine impurities.

The second observation stated that "Validation of production processes, cleaning procedures, analytical methods, and in-process control test procedures are not always adequate…e) you do not have validated cleaning procedures. Cleaning procedures for reactors W02-203-1 AND W02-204-3 in workshop W02, used in the manufacture of crude Valsartan, are not validated in that you do not have data to demonstrate the cleaning procedure is effective following manufacture of 100 consecutive batches…. The fifth observation also identified deficiencies in cleaning procedures. As described herein, ZHP stated in its TEA DIR that the valsartan API manufactured with the TEA with sodium nitrite quenching process was likely cross-contaminated with NDMA due to shared production equipment also using the zinc chloride process which created NDMA. The failure to adequately clean the equipment and validate that cleaning, including an assessment of the chemical reactions and potential impurities including genotoxic impurities in order to test for those potential impurities, constituted a CGMP violation in connection with every batch manufactured for sale.

The third observation identified issues with the validation program. FDA stated that manufacturing processes were not always consistently meeting quality specifications and investigations were not being performed to get to the root cause of the out-of-specification results. As a matter of CGMPs, the investigation to ascertain the root cause for the failure is critical to ensure proper corrections are made to prevent recurrence and provide consistent, reliable product. This process, known as Corrective and Preventive Action (CAPA) is a requirement of ICH Q10, Section 3.2. and is one of the six Quality Subsystems identified in FDA's Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, Section III.D. CAPA is a system for analyzing, correcting and preventing product, testing or process issues. It outlines procedures to identify and analyze the root cause of a problem, to prevent its recurrence. The observations listed on the Form FDA 483 continued to have the common thread of not following CGMPs and not performing risk assessments as required by the regulations, on an ongoing basis.

On August 26, 2018, ZHP sent a response letter to the FDA 483, Inspection Observations, issued as a result of the "For Cause" inspection performed by FDA July 23-August 3, 2018. ZHP's opening paragraphs discuss the inspection for the NDMA impurity and why it was not detected or considered during the process change from the TEA process to the Zinc Chloride process. ZHP went on to state "This particular scenario of unexpected NDMA formation would likely not to be anticipated or envisioned from current perceptible… Based on FDA as well as ICH guideline principals, an unknown impurity below the identification threshold of ICH guidance would be assumed as a regular impurity, and hence controlled as a regular unknown impurity, either specified or unspecified."

As previously discussed, and addressed with ZHP witnesses in the depositions summarized above, a threshold approach should not be used to determine the presence of genotoxic carcinogens including N-Nitroso compounds that are part of the cohort of concern, or the amount of NDMA that would be acceptable in the API or drug product. As a result, ZHP's explanation in the FDA 483 response letter that the NDMA was "below the identification threshold" is an inadequate response contrary to CGMPs. Application of this deficient CGMP methodology by ZHP resulted in the failure to test for NDMA or NDEA with the at-issue manufacturing processes, during development and once the drug product was manufactured for sale, and resulted in the manufacture and sale of adulterated product by definition. Additionally, ZHP goes on to state that "In the current NDMA event, it is not the residual DMF that reacts with nitrous acid of the next step, but rather it is the trace amount of dimethylamine, an impurity/degradant of DMF that reacts with nitrous acid to form NDMA, which adds a further dimension over the current thinking, logic, and strategy for the evaluation of potential genotoxic impurities. It is this extra dimension over the current industry practice that obscured us from foreseeing this impurity during the process change from "Triethylamine process" to "$ZnCl_2$" process." This explanation illustrates the invalid explanations provided by ZHP for its manufacture of the contaminated valsartan, which are not tethered to CGMPs or science. This explanation for not performing testing to identify NDMA impurities was rejected by the FDA as described herein, and as set forth herein was refuted by the scientific literature referenced by Dr. Hecht, and shown to ZHP witnesses during their depositions, including for example Mr. Gu's testimony, where he acknowledged that the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" stated in part: "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA." (4/5/21, 65:3-65:24).

ZHP responded to the Warning Letter (320-19-04) described above on December 26, 2018. The Warning Letter summarizes significant deviations from CGMP for the API. There were two areas of concern cited in the Warning Letter:

> #1-Inadequate complaint investigation of unknown peak received June 6, 2018
> #2- Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

ZHP's response included a statement on CAPAs being implemented internally as investigations and assessments progress for better control and mitigation of the risks NDMA and other potential mutagenic impurities have on their products. ZHP also explained that they performed a four-stage investigation, performing systematic risk assessment for the NDMA impurity formation for all related APIs. The response further explained other factors that may have contributed to the presence of nitrosamine impurities as "process impurity/contaminate/cross-contaminates that were included in the later stages of the investigation, including potable water, shared equipment solvent recovery etc. These are all the products of fundamental CGMP violations.

FDA sent a letter to Jun Du February 6, 2019 with concerns regarding ZHP's Warning Letter (320-19-04) response dated December 26, 2018. The letter went on to state that FDA will make a final CGMP status determination after they received additional information. The eleven-item information requested included laboratory testing for the amount of NDMA or NDEA in lots already in U.S. distribution, a toxicological evaluation of the additional nitrosamines (Impurity K, NDBA and NMP-NO) identified in ZHP's risk assessment, a commitment to make changes to the API manufacturing process to prevent nitrosamine formation, a commitment to conducting additional full GC-MS scans on residual solvents for API processes which are currently intended for the US. Market, as well as additional laboratory investigations, analyses and reports related to the NDMA and NDEA contamination of the API.

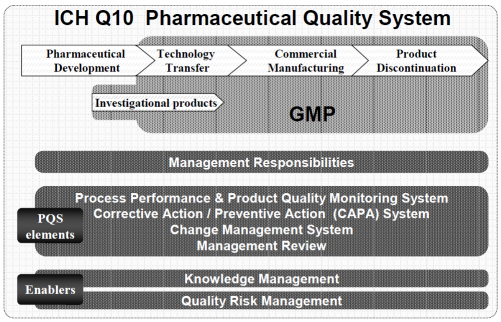
ZHP responded to FDA's February 6, 2019 request for additional information related to their Warning Letter response. I have reviewed this response of more than 200 pages. The responses do not adequately respond to the fundamental deviations identified by the FDA. Rather than accepting responsibility for a massive CGMP failure that resulted in dangerous gentoxic contamination of blood pressure medication, ZHP makes excuses and fails to acknowledge that its failures were attributable to fundamentally flawed risk assessment/risk management by its quality assurance organization and high-level management, which was ongoing throughout the entire lifecycle of the drug product.

In a letter dated April 14, 2019, ZHP responded to FDA's February 6, 2019, requesting additional information related to their Warning Letter response. ZHP's extensive response details the testing performed to identify NDMA and/or NDEA in their all batches of their API still within expiry or were labeled "retest by" date. ZHP explained they still had not completed method development for their GC-MS/MS instrument, but "commits the specification of both NDMA and NDEA will be soon updated to "Less than LOD" as not detectable level for further releasing. Once such method validation completed with LOD/LOQ comparable to FDA's published method, the specification of ARBs will be tightened to not detectable level of NDMA and NDEA for releasing control and it will be submitted to the agency by technical amendment to each DMF." The response continues with the root cause determination for the NDMA formation as the TEA process with quenching, as well as potential contamination due to cross-contamination from different processes using a shared production line. Additionally, ZHP stated there was also cross-contamination introduced by shared solvent recovery equipment. In my opinion, there continued to be an ongoing lack of commitment to CGMP regulations and risk

analysis for their manufacturing operations. In their "Summary of Actions Taken to Prevent Nitrosamine Impurity Formation for Valsartan API", ZHP discussed modifying the process again to separate product before quenching with nitrous acid. The quenching ould be performed off-line to reduce the chance of NDMA formation.

According to ZHP's Warning Letter response, on May 22, 2018, Novartis asked Huahai to provide information about the unknown peaks eluted near the toluene peak in the residual solvents. The complaint investigation was completed and documented in CC-18004, which was provided to Novartis on May 31, 2018, titled Study Report of Unknown Peak in Residual Solvent of Valsartan, ZHP01870977. ZHP goes on to state Novartis then provided more batches related to the same complaint. A second investigation response was provided to Novartis on June 4, 2018, titled Study Report of Unknown Peak in Residual Solvent of Valsartan, ZHP00021455, inaccurately concluding on page 8 of 8: "The unknown peaks in residual solvent of Valsartan are far lower than the ICH limit of each solvent through quantitative analysis. The product quality is less likely to be impaired." ZHP believed the investigation reports had addressed Novartis' concerns.

However, two days later on June 6, 2018, Novartis notified ZHP the unknown peak had been identified as NDMA using a gas chromatography-mass spectrometry (GC-MS) method, a well-established method, performed by Solvias, a third-party contract laboratory commissioned by Novartis. This is approximately one-year after ZHP's knowledge of the NDMA in valsartan had been referenced in an email sent July 27, 2017 to Dr. Min Li and other ZHP employees from Jensheng Lin, an employee of CEMAT. As stated above, Mr. Lin's role included impurity identification, including mechanisms, in their API and finished dose product. ZHP's responses evidence clear violations of CGMP, and demonstrate the deficient approach of ZHP to CGMP throughout. ZHP's responses to Novartis were demonstrably inadequate and incorrect, as Novartis demonstrated by identifying the NDMA, and ZHP should have immediately notified FDA of the genotoxic carcinogen (NDMA) detected in the API and finished drug product as soon as it was known. As set forth herein the FDA disagreed with ZHP's assertion that they could not have been expected to foresee or detect the NDMA due to a "knowledge gap". Knowledge Management and Quality Risk Management are two major features found in ICH Q10, Pharmacy Quality System model (see diagram below), and are an expectation of FDA throughout the entire product lifecycle. These CGMP duties were violated.



FDA performed another "For Cause" inspection of the ZHP Xunqiao, Linhai, Zhejian facility May 20-31, 2019, resulting in six (6) Inspectional Observations. These issues related to ZHP's efforts to address the now known CGMP violations that led to the NDMA and NDEA in the ZHP API and finished dose to begin with. The first and most egregious observation was for lack of appropriate validation of analytical methods for GC-MS analysis of NDMA and NDEA. This is a violation of 21 CFR 211.165(e) which states "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented." Lack of appropriate validation of the GC-MS method calls into question all testing performed using that method. Test results may not be accurate or reproducible. On August 16, 2019, FDA notified ZHP the "For Cause" inspection May 20-31, 2019 was again classified with the most severe inspection classification, Official Action Indicated (OAI), regulatory and/or administrative actions will be taken. (PRINSTON00157232). This was the second OAI classification received by ZHP in less than one year. The first OAI classification resulted in a Warning Letter and the Import Hold Alert. These are significant actions, and the repetition twice within one year demonstrates that ZHP was in a state of significant CGMP non-compliance at the subject facilities throughout, which technically renders any product produced in those facilities to be adulterated. 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 351(a)(2)(B). However, here there are also numerous CGMP violations specific to the manufacturing of the subject drug product so it is not necessary to resort to the general overarching non-compliance with CGMPs to establish adulteration by definition.

On September 4, 2019, FDA Compliance Officer Rory K. Geyer issued a letter to Jun Du referencing ZHP's April 14, 2019 Warning Letter response, noting ZHP committed to a retrospective assessment of residual solvent chromatograms for all APIs produced by ZHP to identify the unknown peaks. ZHP provided data for five (5) API products committed to have the review completed for angiotensin II receptor blocker (ARB) related APIs completed by September 30, 2019, and the non-ARB API review completed by December 31, 2019 and asked for an update on ZHP's progress. Additionally, FDA asked ZHP to inform them of their readiness for a reinspection and a statement of readiness from their independent third-party consultant. FDA also asked for ZHP to indicate whether all Warning Letter remediation action items previously committed to were complete and for those action items still incomplete, to provide an estimated completion date.

ZHP responded on September 25, 2019 to FDAs September 4, 2019 letter stating they were ready for re-inspection and provided a copy of the audit report performed by their third-party consultants. The conclusion provided by the consultants did not confirm readiness for an FDA audit, but rather stated ZHP had "improved their quality management system, specifically, established good risk assessment approach to new process or any process change in order to identify and prevent any possible genotoxic impurity to ensure the product quality in the future". (ZHP00397222). ZHP's response went on to state they completed a full scan GC-MS analysis of APIs manufactured at the Channan facility in 2018. The response went on to state they had been, "continuously performing the investigation per the established plan and now we have completed the investigation of all the unknown peaks with S/N>10 observed in the GC-FID methods of residual solvents for all the historical production batches of 5 sartans (up to August

2019) within expiry (refer to the table below), except for batches of year 2018, the investigation of which had been completed and submitted to the Agency dated April 14, 2019." (ZHP00397222)

On September 26, 2019, FDA's Office of Manufacturing Quality requested a face-to-face Regulatory meeting with ZHP. The purpose of the meeting was to discuss ZHP's risk assessment addressing the use of recovered solvents during API production which may contain residual material (including solvents) from use of common equipment and lack of cleaning between batches, ZHP's retrospective review of unknown peaks, an overall assessment of deviation investigations, atypical complaints, out-of-specification results, and failures, among other information related to production of the API. The face-to-face meeting between ZHP and FDA was held November 7, 2019 resulting in a 13-item list of action items requested by FDA. FDA requested ZHP respond to the list of action items by December 2, 2019. ZHP agreed to respond to the action item list on November 21, 2019, a full two weeks later after receiving the list from FDA.

A "For Cause" comprehensive CGMP follow-up inspection to Warning Letter 320-19-04 was performed by FDA July 19-29, 2021 at the Chuannan manufacturing facility for non-sterile API. The inspection report states: "Management indicated, and I confirmed that they have not distributed directly product into the US market since August 2018. Between 2018 and July 2021, the firm has manufactured APIs (Valsartan, Losartan Potassium, Irbesartan, etc.) for research and development (R&D) and supplied it to domestic customers that subsequently may have manufactured finished drug products for distributing in the US market."

The inspection verified corrections to all objectionable conditions and found that corrective actions to the FDA-483 items and Warning Letter were adequate. No FDA-483 Inspectional Observations was issued during this inspection and the inspection was classified "No Action Indicated" (NAI), which means no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action). Food & Drug Administration, *Inspections Database Frequently Asked Questions* (May 11, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions; Food and Drug Administration, *FMD 86: Establishment Inspection Report Conclusions and Decisions* (Jan. 28, 2014), https://www.fda.gov/media/87643/download.

The October 18, 2021 letter from the FDA confirming that ZHP was NAI after the July 19-29, 2021 inspection indicated in part, "This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with cGMP." (ZHP02736683).

Based on the NAI classification of the FDA audit performed July 19-29, 2021, ZHP submitted a petition to FDA on October 26, 2021 for expedited removal of Zhejiang Huahai Pharmaceutical Co., Ltd. (FEI: 3003885745; Site Address: Chuannan, Dugiao, Linhai, Zhejiang 317016, China) and its products from Detention without Physical Examination (DWPE) under

Import Alert #66-40. FDA sent a response letter to ZHP November 10, 2021 informing the DWPE under Import Alert #66-40 stating ZHP had met the criteria for removal from DWPE.

November 4, 2021, FDA submitted a Closeout Letter (MARCS-CMS-566685) to ZHP notifying them that FDA completed an evaluation of the corrective actions in response to Warning Letter 320-1-04, dated November 29, 2018, and based on their evaluation it appeared ZHP had addressed the deviations cited in the Warning Letter. FDA stated "future FDA inspection and regulatory activities will further assess the adequacy and sustainability of the corrections" and that "this letter did not relieve you or your firm from the responsibility of taking all necessary steps to assure sustained compliance with the Federal Food, Drug and Cosmetic Act and its implementing regulations or with other relevant legal authority." (ZHP02736709).

David Chesney

I have reviewed the report and deposition of ZHP's CGMP expert David Chesney, addressing only the zinc chloride process used to manufacture valsartan API, not addressing the TEA with sodium nitrite process or ZHP's manufacture and sale of valsartan finished dose. (David Chesney Dep. Tr. 24:1-6, 324:10-14). In his deposition, Mr. Chesney described the November 2018 FDA Warning Letter to ZHP, and agreed that it, "summarizes significant deviations from current good manufacturing practices (CGMP) for active pharmaceutical ingredients (API)." (David Chesney Dep. Tr. 320:24-321:6).

Mr. Chesney confirmed that if the risk assessment conducted by ZHP was in violation of CGMPs, "it [would] be a violation of GMP to then manufacture with that manufacturing process which is creating NDMA." (David Chesney Dep. Tr. 114:12-115:3). Mr. Chesney also agreed, "[R]isk assessment is not a static process, it's a process that continues through the lifecycle of the drug's production and manufacture," and "[i]f they are aware that a product contains a contaminant that poses an actual or potential danger to health, and tell no one and continue to ship it anyway, that could be construed later, after evaluation of all the facts, as having shipped a contaminated and, therefore, adulterated product in interstate commerce." (David Chesney Dep. Tr. 189:24-190:3, 195:16-23). As stated herein, CGMP is an ongoing obligation for the lifecycle of the product, and I agree with Mr. Chesney that each use of the manufacturing process without performing an adequate risk assessment in violation of CGMPs, and failure to test and identify the NDMA and NDEA in each manufactured batch produced with the zinc chloride and TEA with sodium nitrite quenching processes constituted an independent set of CGMP violations.

Mr. Chesney confirmed, "[t]he failure to adequately assess the potential formation of mutagenic impurities when ZHP implemented the new process, that would be a CGMP violation." (David Chesney Dep. Tr. 329:9-331:16). Also, as stated by the FDA in the Warning Letter, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change." Mr. Chesney agreed this was a CGMP violation. (David Chesney Dep. Tr. 331:17-332:5). In this connection, he also agreed with the FDA as to the scope of ZHP's duties: "You are responsible for developing and using suitable methods to detect impurities when

developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." (David Chesney Dep. Tr. 332:7-21). Related, the FDA noted, "We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce," and Mr. Chesney agreed that this was ZHP's responsibility. (*Id.* at 335:12-336:2).

Mr. Chesney was also asked about the FDA's discussion of "ghost peaks," and the "[f]ailure of [ZHP's] quality unit to ensure that quality-related complaints are investigated and resolved." (*Id.* at 321:21-322:4). As stated by the FDA, "Our investigation also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms." (*Id.* at 326:2-7). The FDA stated:

> …"Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was expected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further."
>
> * * *
>
> …"FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation."

(*Id.* at 326:8-328:3). Mr. Chesney testified that due to his lack of scientific expertise, he could not give an opinion on this issue. (David Chesney Dep. Tr. 318:3-17). However, he did agree that, "if you identify either the potential or the actual occurrence of [a genotoxic] impurity, then certainly it's important to understand it." (David Chesney Dep. Tr. 134:22-135:15). In this context, Mr. Chesney agreed that if one were to assume that ZHP is correct that there was not an available analytical method to test for and establish that the unknown peaks on the gas chromatography were due to NDMA (or NDEA) or another genotoxic impurity in the valsartan prior to June 2018, then one could not sell the drug product while knowing that there was the potential for an unknown unreasonably dangerous impurity: "You should not go forward unless there's a persuasive reason to believe that the formation of these impurities would be at such a low level that it would not present a risk to human health." (David Chesney Dep. Tr. 167:2-21). Based on the materials discussed herein, those methods existed and definitive testing was feasible and should have been employed by ZHP.

Finally, Mr. Chesney confirmed that the responsibility for quality deficiencies is an executive responsibility, "the leaders of the company, right up to the highest executive, would have the ultimate responsibility for this quality problem," and with regard to the July 27, 2017 Jinsheng Lin email, "as a matter of GMP that the information in this e-mail could not be ignored; it needed to be aggressively evaluated by the so-called, quote-unquote, leaders as soon as it was brought to their attention." (David Chesney Dep. 229:22-230:1, 230:9-16). Mr. Chesney was questioned about an article he authored titled, "Executive Responsibility for Quality," in the book titled, "Quality Management Essentials, Expert Advice on Building a Compliant System." (David Chesney Dep. 233:22-234:10), which stated in part:

> Executive commitment to quality in the pharmaceutical industry is critical, not only to ensure continuing profitability of the company, but also for the safety and well-being of patients and to meet the needs of healthcare providers who prescribe and use pharmaceutical products every day.
>
> * * *
>
> For these reasons, quality assurance (QA) and GMP compliance may be viewed differently in the pharmaceutical industry than in those industries where a reputation for high quality drives sales. Quality assurance may be viewed as a 'cost of doing business' or an internal 'police department' issuing directives that delay or prevent product release. That viewpoint can result in a low priority being assigned to quality operations and resourcing, which can lead in turn to quality problems, regulatory difficulties, unnecessary expense, adverse publicity, lawsuits and investor disappointment. All these consequences are preventable if executive managers understand the importance of the quality assurance function and treat it as a critical business operation just like other critical areas, such as strategic planning, financial management and others.
>
> * * *
>
> In addition to the business benefits, health regulatory agencies around the world both require and expect top management to support a strong quality assurance function for their companies.

(David Chesney Dep. 234:24-235:9, 236:23-238:11). Mr. Chesney confirmed that, "[t]op management would include, for example, the chairman of ZHP, Mr. Baohua Chen; he would fall within the context of top management." (David Chesney Dep. 238:7-10). Mr. Chesney's article also lists, "Common Mistakes Executive Teams Make," including, "Emphasizing production quotas and market demands to the extent that quality problems are overlooked or regarded as unimportant - worst case, deliberate coverup of known quality problems through falsification of

records." (David Chesney Dep. 247:24-248:14). Mr. Chesney unequivocally testified with regard to the executive responsibility for the failure to discharge quality duties:

> [T]here's a "growing consensus about the most critical quality management concepts. First among those is that executive management teams are the key to a company's ability to successfully meet quality standards on a consistent basis. Doing so is critical to proper clinical performance of the products of this industry and therefore, ultimately, to global public health."
>
> And you would agree that within ZHP, the ultimate responsibility lies with the executive management team, correct?
>
> * * *
>
> A. Yes, I would agree it applies to ZHP and everybody else in the industry.
>
> * * *
>
> The last paragraph of this article says, "Prudent management teams recognize this and support their quality units both philosophically and materially, with strong policies backed up by consistent actions, authority and resources. Failure to do so may have both serious business consequences for the company and potentially even personal consequences for individual executives."
>
> Again, that's a statement that you believe would hold true for ZHP and any company in this industry, right?
>
> A. Yes, any company in this industry.

(David Chesney Dep. 251:11-252:20). Mr. Chesney agreed that "It would never be acceptable for ZHP or any other company to place profits over safety." (David Chesney Dep. 235:14-18).

I agree with Mr. Chesney's description of the quality duties. Based on Dr. Hecht's report and the deposition testimony from ZHP's witnesses and the scientific literature they were questioned about, it is my opinion as set forth herein that these failures by ZHP, admitted or nearly admitted with a caveat as to available scientific knowledge, did constitute repeated violations of CGMPs with regard to both the zinc chloride and TEA with sodium nitrite quenching processes.

CGMP Violations Related to the Zinc Chloride Process

ZHP committed a number of CGMP violations in connection with the manufacture of valsartan API with the zinc chloride process, which are discussed throughout this report. I focus here on summarizing those that are most significant and responsible for the NDMA impurity in the valsartan API manufactured with the zinc chloride process, and relative to the manufacture of the valsartan finished dose using the valsartan API containing NDMA. These and other violations are catalogued and discussed by the FDA and in the ZHP deviation investigation reports, and in the testimony and documents referenced herein and the attached list of materials reviewed.

ZHP was permitted to satisfy its CGMP obligations by enacting and adhering to appropriate internal protocols to be followed in order to assure compliance. ZHP did enact various applicable internal protocols, however ZHP failed to follow those protocols to the extent that they existed, resulting in the CGMP violations that led to the NDMA and NDEA impurities.

ZHP's process change was conducted in violation of CGMPs. SMP-018.01, titled Change Control System, had an effective date of June 15, 2011. (ZHP00469139-162) and the Change Request Form template is attached and this is the version utilized by ZHP in connection with the change to the zinc chloride process. The next revision, SMP-018.02, was effective on April 15, 2012, and is substantially the same with no material differences. (ZHP00246632-647). SMP-018.01 stated its purpose in section 1: "The purpose of this SMP is to ensure all the changes that will impact the quality of products, standardize the change control process, to manage changes related to product quality and process, including the change initiation, assessment, approval, implementation and close to ensure compliance to CGMP, EHS AND ICH Q7 requirement. Avoid error of quality incident." Section 2, Scope, stated: "This SMP applies to all planned changes related to GMP, EHS and manufacturing, such as equipment changes that may impact product quality and safety, process changes, and changes on validated system and other GMP systems. This SMP is powerful in Huahai Xunqiao site, Chuannan site and formulation site. Unplanned change should be regarded as deviation and handled according to 'Deviation Investigation Management System SMP-017." Section 3 defines a Change as, "A change difference planned to make which has direct or potential impact on product quality, manufacturing process or EHS, intend to give a planned change on existing GMP or EHS system." Section 4.1.1 provided that "If it is a critical change, feasibility report should be provided." The changes to both the zinc chloride and TEA with sodium nitrite quenching processes were critical changes. Section 6, titled Procedure, begins with 6.1 titled Fundamental Principle, and stated in 6.1.1: "All planned changes to manufacturing processes, GMP equipment, GMP automated systems or GMP facilities must be evaluated to determine any impact to product quality and EHS." Thus, this SMP applied to the process change to the zinc chloride process (and to the prior change to the TEA process with sodium nitrite quenching), and was intended to ensure product quality. The SMP was not complied with in both process changes, resulting in the manufacture and sale of valsartan API (and valsartan FD) containing NDMA and NDEA.

Section 6.1.5 spells out core obligations under this SMP: Each change request is to consider the potential impact to related change control systems and risk assessment such as analytical methods, automation, sampling/testing, SOP's, retest dating, contractor management and in-process controls, labeling and manage and document the resulting impact (via those related systems) accordingly. **The risk assessment includes whether the change control will cause any new risks and these risks will be controlled or eliminate by suitable preventive action**.

Section 6.1.7 provided: **The change request must be discontinued if upon implementation the process** fails to perform within established critical process parameters, **fails to meet critical quality attributes**, or is unable to meet validation acceptance criteria required to support the change. The change procedure must be started and reassessed if necessary.

Related, Section 6.3.5 also provided that, "QA shall review the change action of the CR form and completion situation…QA shall close the CR and archive the change files when all the actions completed and meets expectation. **QA shall reject the change request if the action cannot meet predetermined expectation**…" Section 6.3.7 provided: "If the change can't be approved by the change control committee, the change will be a refused one; the refuse reason must be documented on the request form and signed by the party that did not approve the change request, then pigeonhole it."

Also relevant, where ZHP was selling the valsartan API to finished dose customers Torrent and Teva and finished dose to Prinston pursuant to a Quality Agreement, Section 6.3.8 provided: "If any change is planned during contract manufacturing business, the change only can be taken place upon the approval of client in advance." Version 2 added one provision here, and provided in subsection d, "The judgment basis of informing customers/authorities is listed in attached form (Q/ZHH JG-194)." The Change History confirmed that this was the only modification from Version 1 of this SMP. ZHP had quality agreements in place with Prinston, Teva and Torrent, obligating ZHP to comply with its CGMP obligations. (TEVA-MDL2875-00020279 (TEVA 167); TEVA-MDL2875-00020213 (TEVA 168); TEVA-MDL2875-00020214 (TEVA 169); TEVA-MDL2875-00020212 (TEVA 170); TORRENT00536415; TORRENT00291332).

Section 6.2.1 differentiates between a Critical and Minor Change, defining a Critical Change as "A change which has direct or potential impact on product identity, strength, quality, purity and regulation, or have impact on validated Procedure, method, qualification or equipment." The change to the zinc chloride process (and to the TEA process with sodium nitrite quenching) was designated a Critical Change.

Another relevant protocol was API-R&D-002, titled Guideline for API Developing – Guideline for Genotoxic impurity Evaluation. (ZHP01447235-242). According to the deposition of Peng Dong this was dated June 17, 2011. He confirmed that Section 2, provided that, "All intermediates and APIs produced under GMP conditions must be identified for genotoxic impurities," and per ICH the risk assessment evaluation included identification of genotoxic impurities and confirmation of the quality specifications of any API, including valsartan. In addition, the SOP provided for pilot scale testing as part of the process. (3/29/21, 33:9-34:10,

41:14-42;1, 61:24-62:16). This internal protocol was violated, and as with the other violations of internal protocols this constituted a CGMP violation.

Another important internal protocol was SMP-023, titled Quality Risk Management. Per version SMP-023.03, the initial version was effective on September 1, 2011. (ZHP00000417). The purpose described on page 2 of 16 included ensuring "effective and consistent risk based decisions regarding the quality of products across the product lifecycle." It was applicable to Xunquiao and Chuannan, and applied to the "whole lifecycle of drug substances and drug (medicinal) products…". It provides on page 3 of 16 that the "quality risk management process…should be based on scientific knowledge," and continuous improvement and enhancement capabilities should be integrated into the quality risk management procedure." Also, on that page the product lifecycle is defined as: "All phases in the life of the product from the initial development through pre-approval and post-approval until the product's discontinuation." On page 15 of 16 references are listed including ICH Q9, WHO Guidelines of Quality Risk Management, and 2010 GMP Guidelines. This comprehensive standard operating procedure (SMP) sets forth a CGMP based approach to identification and management of risks. If this SMP had been followed and applied as intended, the risk of nitrosamine would have been identified and testing to identify the NDMA and NDEA would have been performed. ZHP failed to comply with this SMP, in violation of CGMPs.

The Valsartan Impurities Profile Analysis Report dated April 10. 2012 stated that it included "systematic, scientific and comprehensive illustration of the impurity profile for Valsartan…The specifications for intermediates and final drug substance Valsartan are established according to batch analysis results and related pharmacopeia monographs of Valsartan." It compared the TEA process without sodium nitrite quenching and the zinc chloride process, and provides schematics demonstrating each process. Section 5 Re-evaluation for Potential Impurities provided for re-evaluation where, "(1) The manufacturing process is changed, (2) The unevaluated unknown impurities are present in the drug substance for successive batches." The Conclusion was that "The specifications of starting materials and intermediates are reasonable, and the quality of Valsartan is stable and acceptable." However, there is no reference to NDMA or any nitrosamine as a potential impurity. (ZHP00476862-909).

ZHP failed to comply with its own internal protocols, in addition to the other sources of authority as listed and discussed in this report, failing to conduct an adequate risk assessment of the zinc chloride manufacturing process at any time. Specifically, ZHP failed to adequately evaluate the potential chemical reactions and formation of impurities during the process, and as a result failed to recognize the potential formation of nitrosamines including NDMA.

The inadequacies in the risk assessment are well-documented. The failure to conduct an adequate risk assessment, and consequent failure to recognize the potential formation of nitrosamines including NDMA from the outset was followed by further ongoing CGMP failures including the failure to test for nitrosamines including NDMA as part of the deficient process validation, and the failure to establish specifications and testing methodology to ensure that nitrosamines would be tested for and excluded in all manufacturing batches, as a matter of

course and in response to observations of unknown peaks both internally and by customers, and then to test and identify the NDMA. If ZHP had identified the potential formation of nitrosamines including NDMA during a risk assessment at any step of the way, and tested for NDMA using available technology (GC-MS or similar methods per Dr. Hecht), the NDMA would have been detected and the zinc chloride process as utilized by ZHP could not have been utilized for the manufacture of valsartan API. In this connection, ZHP's documented knowledge that there was NDMA in valsartan, and the root cause which applied to sartans (quenching with sodium nitrite in the presence of the drug product), at least as of July 27, 2017, and inexplicable decision to continue marketing that API without disclosure to any customer or regulatory authority, was a further violation of CGMPs.

In this context, I have seen indications in ZHP's communications with the FDA and in certain deposition testimony that ZHP has argued that the potential formation of nitrosamines and methods of testing to identify nitrosamines was not known or available during the development of the zinc chloride process. This argument was rejected by the FDA, as set forth above. In addition, as set forth above, the inadequate knowledge and research by ZHP was recognized in a draft of a deviation investigation report by ZHP. The FDA's statement and the acknowledgment in the draft DIR, are consistent with Dr. Hecht's opinion, and the deposition testimony of Peng Dong and Min Li, and others, establishing that knowledge of the chemical reactions that led to the formation of NDMA, and the mass spectrometry needed to test for nitrosamines, was available and well known in the scientific community well before the time that the zinc chloride process was developed and then implemented for commercial manufacturing. Ultimately, as agreed to by ZHP's CGMP expert Mr. Chesney in his deposition, if ZHP had identified the potential formation of nitrosamines but hypothetically did not have the means to test to be sure nitrosamines were not forming, then ZHP could not utilize that process anyway since one could not utilize a manufacturing process that could be creating a genotoxic impurity without first confirming that no such impurity was forming. (David Chesney Dep. Tr. 167:2-21).

In addition, ZHP failed to adequately evaluate the unknown peaks seen on gas chromatography performed by ZHP and several of its API customers. This duty existed before and after ZHP began to manufacture for commercial sale. ZHP was required to evaluate those peaks, to ensure that they were not indicative of a quality issue that required action. ZHP's apparent rationale for not taking the required steps was that the peaks were below the level requiring action. However, this was not a valid excuse, since it was known that potential "cohort of concern" impurities could be genotoxic and thus not be subject to the thresholds applicable to other potential impurities. As set forth above, n-nitroso compounds, which includes NDMA and NDEA, are part of the "cohort of concern" and thus not subject to the "threshold of toxicological concern" approach. Instead, each such substance must be evaluated independently in context, as ultimately occurred once the FDA became aware of the NDMA and NDEA in ZHP's valsartan. This failure also has its roots in the ongoing inadequate risk assessment and quality risk management since recognition of the potential formation of nitrosamines would have required the use of appropriate testing methods as described above, which would have swiftly resulted in identification of NDMA. This is what occurred when Novartis was unwilling to accept ZHP's assurances that the size of the unknown peaks rendered them of no concern, as late as June 4,

2018, two days before Novartis confirmed that the peak was due to NDMA. Again, this is aside from the documentation indicating that ZHP already knew that there was NDMA in the valsartan and the root cause no later than July 27, 2017.

Finally, the July 27, 2017 email sent by Jinsheng Lin, Ph.D. to a number of people including Min Li, Peng Dong, Jucai Ge, and others, presents additional CGMP violations, and likely violations of the FDCA. This document was never mentioned by the FDA, and was presumably unknown to the FDA. Dr. Lin addressed an impurity that was identified during development of a potential alternative manufacturing process for irbesartan, another sartan, and noted that what was being seen was similar to the NDMA in valsartan, formed due to sodium nitrite quenching. As stated above, this is exactly the type of information that Dr. Lin was employed to identify and know, and it was scientifically correct.

It is fundamental that ZHP was not permitted to keep this knowledge secret and continue to utilize the zinc chloride process to manufacture valsartan API to be marketed, or the TEA with sodium nitrite process for that matter, since that was among the sartans manufactured with sodium nitrite quenching. The continued use of that manufacturing process once the presence of NDMA and root cause was known was a violation of CGMPs, and this violation impacted every pill manufactured and sold with that process, just as the CGMP violations repeated over and over with the manufacture of batch after batch impacted every pill manufactured and sold with that process from day one. Moreover, doing so with actual knowledge of the genotoxic impurity is a violation of both CGMPs and the FDCA. The sale of adulterated drugs is prohibited. The knowing sale of adulterated drugs, especially those contaminated with genotoxic impurities that are probable human carcinogens, while failing to disclose this information to patients, customers, and regulatory authorities, is a violation of law, and likely criminal.

In addition to the CGMP violations as an API manufacturer, ZHP also violated CGMPs in its role as a finished dose manufacturer. As a finished dose manufacturer, ZHP was required to comply with its internal SMP's and with the requirements of its Quality Agreement with Prinston Pharmaceuticals, to which ZHP sold the finished dose for sale and distribution via Solco, as well as its quality agreements with other API customers. ZHP violated its obligations.

As a result of these gross deviations from CGMPs, as well as the deviations related to cross-contamination, the valsartan API manufactured with the zinc chloride process and finished dose pills using that API were not the approved form of valsartan, as the ANDA, the pharmacopeia, and the labels and package inserts did not include or approve of the presence of NDMA or NDEA (to the extent this was also detected on testing) in the drug product. The pills containing the NDMA and NDEA were adulterated and not legally sold by definition.

CGMP Violations Related To The TEA With Sodium Nitrite Quenching Process

The fundamental CGMP violations with regard to the TEA process with sodium nitrite quenching largely mirror the violations with regard to the zinc chloride process. These include the failure to conduct an adequate risk assessment at any point in time, beginning with the

development of the manufacturing process, continuing through process validation, and the testing of product before and after submission of the DMF and filing and approval of the ANDA filed by Torrent to sell valsartan manufactured with this API. At all points in time the potential for creation of NDEA and NDMA was required by CGMP to be identified, and testing capable of revealing the presence of NDEA and NDMA was required to be performed to address these potential genotoxic impurities. The potential chemical reactions leading to the creation of nitrosamines were well understood, and should have been considered from the outset and throughout. In addition, the technology to test for nitrosamine impurities existed, was well known, and should have been applied to determine whether nitrosamines were forming. If those steps had been taken as required, the process validation specifications would have included testing for NDEA and NDMA, and the NDEA and NDMA formed during the manufacturing process, as well as that resulting from cross-contamination due to inadequate cleaning of shared production lines would have been identified. ZHP would have then been required to develop an alternative manufacturing process that would not form NDMA or NDEA, and/or not expose the drug product to those genotoxic impurities, and either easily applied solution would have prevented the API from containing the nitrosamines. Moreover, when ZHP knew on or before July 27, 2017 that valsartan and other sartans were subject to formation of NDMA and other nitrosamines due to sodium nitrite quenching, ZHP was required to take the same steps listed above, as well as immediately disclose to customers and regulators this information including the presence of NDEA and NDMA in the drug product.

As a result of these gross deviations from CGMPs, the valsartan API manufactured with the TEA with sodium nitrite quenching process and finished dose pills using that API were not the approved form of valsartan, as the ANDA, the pharmacopeia, and the labels and package inserts did not include or approve of the presence of NDMA or NDEA in the drug product. The pills containing the NDMA and NDEA were adulterated and not legally sold by definition.

Prinston, Solco, and Huahai, U.S.

One source establishing Prinston's CGMP obligations is the Quality Agreement between Prinston and ZHP which provided for those entities to ensure compliance with CGMPs, and allocated the responsibilities between them. This was addressed during the deposition of Hai Wang, discussed above. It does not appear that Prinston ever required that the multiple deficiencies noted in its 2014 audit of ZHP's operations were appropriately remedied, which if true was supposed to result in rejection of any further product to be supplied by ZHP.

In November, 2014 it was apparently decided by the finished dose unit of ZHP that they would start to sell valsartan finished dose in the United States, expecting to need about 20 tons of API annually, and in a back and forth email chain (ZHP00107730) Ada Zhou who worked in ZHP Regulatory Affairs, API Group per ZHP0009775 (ZHP 160) indicated on November 19, 2014, "Our API side initiated the process change for Valsartan about catalyst exchange with Zinc chloride ($ZnCl_2$) from 2012 and submitted to FDA in Dec 2013 to demonstrate equivalence on the API quality." Ada Zhou then stated later that day, "Since FDF will initiate change request asap to involve the optimized process Valsartan API, we'd better have Prinston RA signed change

notification…" Kathy Zhang, former Senior Manager of ZHP's Regulatory Affairs, determined, "For risk management purpose, please keep DMF and MTBE residual solvents as in house test items with **Not Detectable** as acceptance criteria until persuasive amount of data (for example 10 consecutive batches) have been accumulated…**the reason to do so is because these two solvents are introduced at step 4, the final synthesis step, and too close to the end. Even worse is that the official residual solvent method for valsartan is not applicable to test these two solvents. Three validation batch alone can't support no testing for them**." (The bold is in the email). Prinston was correct to question the manufacturing process but did not take further steps to ensure that potential genotoxic impurities had been confirmed as not present.

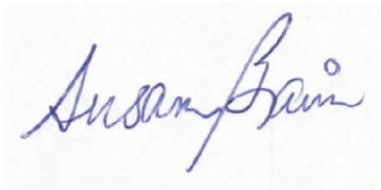
The Change Notification on behalf of Prinston was conditionally signed based on the requirement for the more robust testing for the DMF and MTBE. (ZHP00107734). Of note, the Change Notification that was sent for signature by Prinston (HUAHAI-US00001092) attached Annex 1 with the steps in the process set forth, and indicating that there is no change in the Route of Synthesis. Although Step 4 indicates quenching it does not list sodium nitrite as part of that process. The DMF Amendment does state, "Add quenching procedure after tetrazole reaction with sodium nitrite/HC1 solution." (PRINSTON00079751). Annex 2, the Quality Review, indicates, "The test records of the validation production batches manufactured from optimized process are enclosed to establish the constant quality of Valsartan." and "The items of *new introduced reagent and solvents* are additionally tested for quality review and would not impact the specification." As set forth in detail herein, these statements were incorrect.

As a result of the CGMP violations including the failure to fulfill obligations under the Quality Agreement and potentially per internal protocols, Huahai, US, Prinston, and Solco, sold pills that were represented to be the approved form of valsartan, but in fact were not – instead, they were valsartan containing NDMA, and in some also NDEA. Those pills did not match the description in the original NDA for the brand RLD Diovan or Exforge, the DMF, the applicable ANDAs, the pharmacopeias, or the designation on the label as USP Valsartan. The pills were not the approved formulation of Valsartan and were adulterated by definition.

Conclusion

ZHP, Huahai, US, Prinston and Solco failed to satisfy their duties to ensure that the valsartan API and finished dose manufactured and/or sold by each met the approved identity, quality, and purity of the drug for sale. The CGMP violations described herein, both before and after approval of the applicable ANDA's, resulted in the manufacture and sale of valsartan containing NDMA and NDEA, not the approved valsartan. These process related cGMP deviations, which were present for the manufacture and sale of all pills at issue, resulted in contamination of all pills manufactured with the zinc chloride and TEA with sodium nitrite quenching processes. These violations impacted and economically harmed every person or entity that paid for the contaminated, unapproved valsartan, and exposed each person to the health risks of these probable human carcinogens. The violations of CGMPs in the manufacturing process led to the unacceptable NDMA and NDEA contamination of every pill manufactured with these processes. The valsartan that was sold as the approved form of Valsartan was actually not

the approved form of Valsartan, containing unapproved, undisclosed genotoxic impurities, and meets the regulatory definition of an adulterated drug.



Susan Bain, DRSc

Exhibit A

Susan Bain, DRSc

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EDUCATION

California State Polytechnic University
BS, Biology **1978**

University of Southern California
MS, Regulatory Science **2003**

University of Southern California
DRSc, Regulatory Science **2011**

AWARDS

KGI Outstanding Teaching Service **2014-2015**
Hearst Foundation Grant ($150,000) **2014-2016**

TEACHING EXPERIENCE

University of Southern California **2017-Present**
Assistant Professor, Department of Regulatory and Quality Sciences

Keck Graduate Institute (KGI) **2012-2017**
Professor of Practice; Clinical Regulatory and Quality
Program Director; MBS Clinical, Regulatory and Quality

University of Southern California **2002-2017**
Lecturer; Department of Regulatory and Quality Sciences

RELATED EXPERIENCE

Elsevier
Co-Editor; An Overview of FDA Regulated Products, From Drugs and Cosmetics to Food and Tobacco **2017-2018**

Therapeutic Innovation & Regulatory Science **Ongoing**
Peer Reviewer

PUBLICATIONS AND PRESENTATIONS (RECENT)

An Overview of FDA Regulated Products, From Drugs and Cosmetics to Food and Tobacco **2018**
Co-Editor
Co-authored Chapter on Drugs **2018**

Association of Graduate Regulatory Educators **2017**
Presentation on **Industry Co-Op Experiential Programs**

Parenteral Drug Association **2016**
Presentation on **Visual Inspection Execution & Documentation of Defects and Container/Closure Integrity**

MEMBERSHIPS

Regulatory Affairs Professional Society (RAPS)
Society of Quality Assurance (SQA)
Association of Graduate Regulatory Educators (AGRE)*
Parenteral Drug Association (PDA)
Bio Supply Management Alliance (BSMA)
Orange County Regulatory Association (OCRA)*
*Board of Directors/Officer

PROFESSIONAL EXPERIENCE

University of Southern California (USC); 2017-Present
Department of Regulatory and Quality Sciences
Assistant Professor

- Develop and teach graduate level courses in Quality and Regulatory Affairs to Master's, PhD and Postdoctoral-level students
- Director of Post-Doctoral Master's program in Regulatory Management (MSRM)
- Director of MS Medical Products Quality (MSMPQ)
- Director of Team-based Regulatory and Quality Systems (TRAQS) program
- Executive Board Member of Pharmaceutical Faculty Committee Executive Board
- Member of USC's Health Science Conflict of Interest Review Committee (CIRC)

Claremont Colleges; Keck Graduate Institute, School of Applied Science (KGI) 2012-2017
Professor of Practice and Program Director MBS, Clinical, Quality and Regulatory Affairs; Adjunct Professor of Practice Clinical Sciences; Concentration Coordinator for Clinical and Regulatory Affairs, PharmD Program

- Developed and taught graduate level courses in Clinical, Quality and Regulatory Affairs to Master's, PhD and Postdoctoral level students in an active learning, applied bioscience program, designed to educate students in business, regulatory, quality, clinical and bio-processing, while enhancing their scientific research skills.
- Program Director-related duties, including curriculum development, student mentoring, assessment and associated accreditation activities.
- Faculty member-KGI Curriculum Committee
- Faculty representative to the WASC Accreditation committee for KGI
- Faculty member of the KGI Strategic Planning Committee
- Faculty Advisor for PDA Student Chapter
- Recipient of $150,000 Hearst Foundation Grant for development of the Clinical/Regulatory/Quality program at KGI.

InCompliance Solutions, Walnut, CA **2011-Present**
President/Owner

- Provide highly qualified, multidisciplinary consulting in FDA compliance remediation, process, design, facility, information technology systems, clinical trials and legal areas to the emerging and established biotechnology, pharmaceutical, medical device and diagnostics, active pharmaceutical ingredients (API) and dietary supplement industries.
- Support development of Quality Management System (QMS)/ISO 13485 systems for drug, biologic, medical device and combination product firms.
- Perform CGMP, CGCP and CGLP audits for pharmaceutical, medical device and combination products who are commercialized, under development or in clinical trials.
- Review and approve CAPA responses, resulting from manufacturing operations, complaints and internal, supplier and Agency audits.
- Review and approve non-conformance and deviations generated on clinical and commercial products.
- Team member for development, qualification and validation of new sterile processing drug/biologic and combination product facilities.

SQA SERVICES, Rolling Hills, CA **2010-2012**
Senior Auditor (Contract/Consulting)

- Perform cGMP supplier audits as a 3rd party auditor for major pharmaceutical corporations.
- Review and approve CAPA responses, which resulted from supplier audits for major pharmaceutical corporations.

SpineWorks, LLC, Huntington Beach, CA **2005 – 2012**
Vice President, QA/RA, Operations (2005 – 2012)

- Assured product was developed, contract manufactured, packaged and distributed in compliance with FDA regulations for Class I and Class II Medical Devices and Surgical Tools, while meeting corporate financial goals.
- Managed all R&D projects for new implantable medical devices and surgical tools from project initiation through complete product life cycle.
- Maintained company metrics for Quality Systems related to customer complaints, supplier performance, Corrective and Preventive Actions (CAPA) etc. Reported Adverse Events to FDA.
- Management Representative for company

Director, Quality Assurance (2005 – 2006)

- Designed and implemented complete Quality System documentation in compliance with 21 CFR Part 800 for medical device development, manufacture and licensing with the FDA for Class I and Class II Medical Device Implants and Surgical Tools for a start-up Medical Device company.
- Sourced and initiated R&D and commercial production with contract manufacturers for Class I and Class II implantable Medical Devices and Surgical Tools.
- Interfaced with FDA regarding cGMP audits and compliance issues.
- Received, tracked and reported all customer complaints and CAPA issues

Watson Pharmaceuticals, Corona, CA **2003 – 2005**

Manager, Corporate Quality Assurance (2004 – 2005)

- Initiated and coordinated all product recalls for products manufactured at Watson, Corona facility.
- Maintained working knowledge and interface with FDA for product recalls and recall releases. Tracked all recalled products, ensuring product destruction met FDA guidelines and regulations.
- Tracked sample products to sales representatives.

Manager, Regulatory Affairs (2003)

- Provided regulatory expertise regarding development strategy and regulatory dossier preparation for post-approval product; developed project timelines.
- Provided technical review of all performance/stability data and reports to be incorporated into regulatory submissions to assure scientific rigor, accuracy, and presentation clarity.
- Coordinated, prepared, and reviewed responses to deficiency letters.
- Reviewed adverse drug reactions and complaints, and filed all related reports per FDA guidelines
- Reviewed and submitted all labeling as required per FDA guidelines.
- Maintained strong customer orientation and focus. Served as the Regulatory contact on assigned post-approval products for both internal and external issues, and FDA contact.
- Prepared FDA Annual Reports for approximately 13 product lines, including complaints and adverse events.

U.S. Food and Drug Association (U.S. FDA), Irvine, CA **2002 – 2003**

Consumer Safety Officer

- As a certified Medical Device Investigator, inspected various pharmaceutical, medical devices, IVD, and veterinary medicine firms for compliance to all regulations for product licensure and cGMP compliance
- Investigated consumer complaints against FDA regulated products
- Conducted recalls, audit checks, and compliance to injunctions & seizures either voluntary or FDA mandated.

Porex Medical Products (Medegen), Ontario, CA **1999 – 2002**

Director, Regulatory Affairs and Quality Assurance

- Directed and supervised Quality Engineers, Inspection Supervisors, Document Control functions and Quality Systems in Class II Medical Device Manufacturing.
- Managed all Regulatory Affairs functions including compliance to FDA Medical Device guidelines (QSR's) for development, manufacture, packaging and release of Class II Medical Devices.
- Directed and trained all company personnel on CGMP guidelines and requirements.
- Reviewed/approved all documentation for the development, validation, manufacture, packaging, and labeling of components and finished devices.
- Reviewed corporate compliance status and improved documentation for the development, validation, manufacturing, packaging, and labeling of components and finished devices.
- Implementation and receipt of ISO 9001 Certification of facility and operations.
- All Quality/Regulatory departmental budgets and staffing plus internal and external audits, customer complaints and MRB responsibility, managed FDA Communication and MDR submissions.

- Managed all customer complaints, CAPA activities and Adverse Event reporting to the FDA for the company's medical devices as well as product we produced as a contract manufacturer.

Techniclone Corporation (Peregrine), Tustin, CA **1996 – 1999**

Director, Quality Assurance/Quality Control

- Designed and implemented complete Quality System documentation including SOPs, Raw Material Specifications, Test Methods and Manufacturing Work Orders in compliance with 21 CFR Part 210 and 211 for new drug development and facility licensure with the FDA for murine monoclonal antibody used in cancer therapy.
- Managed QA, QC and Microbiology Laboratories
- Directed, trained and developed personnel in QC testing, audit administration, batch record review for product release, label issuance/accountability, receiving inspection, in-process and final product evaluation, deviations and change control for sterile drug product.
- Received, reported and maintained complaints for clinical trial product. Reported any Adverse Events to the FDA as required.
- Developed/tracked/monitored adherence to departmental budgets in support of over-all company objectives.
- Conducted critical reviews of complex reports, validations studies, and analytical data for scientific merit and CMC submission for IND.

Baxter Health Care Corp., Los Angeles, CA **1994 – 1996**

Manager, Quality Assurance, Raw Materials (1995 – 1996)

- Managed Raw Material Inspection Area; Supervised non-exempt inspectors.
- Sampled, tested, disposed of, and documental all commodities used in the company's products and packaging.
- Developed/implemented inspection procedures; controlled and administered quarantine areas.
- Trained inspectors on performance of raw material aseptic sampling for laboratory analysis.
- Tracked Supplier performance through a supplier rating system and interfaced as necessary.

Supervisor, Quality Assurance, Raw Materials (1994 – 1995)

- Supervised inspection of all raw materials used in the manufacture of Hyland Division products
- Assisted Quality Assurance Mgr. including in training of supervision of non-exempt personnel.

Product Release Coordinator, American Red Cross Products (1994)

- Reviewed and evaluated all documentation associated with the final product release of ARC products.
- Reviewed all manufacturing, Quality Assurance, Quality Control Laboratory and Final Packaging documentation and calculations for each lot prior to release to the marketplace.
- Interfaced extensively with on-site ARC manufacturing planning personnel, & manufacturing managers.

Alpha Therapeutic Corporation (Grifols), Los Angeles, CA **1988 – 1993**

Manager, Quality Control Operations (1990 – 1993)

- Planned, scheduled, and directed the activities of the Quality Control Inspectors and Supervisors engaged in raw material, in-process manufacturing, and final packaging inspection.
- Managed Quality Control for the off-site plastics manufacturing facility; functions included performance evaluations, administration of disciplinary actions, department budgets and planning,
- Represented QC Dept. during on-site FDA, State and international inspections.
- Developed Quality Control Standards, devised, designed, procured, and trained inspectors on test methods and devices required for inspection.

Manager, Raw Material Quality Control (1989)

- Managed the Raw Material Inspection Area and non-exempt inspectors in the sampling, testing, disposition, and documentation of commodities for use in manufacturing and packaging.
- Developed inspection procedures, administered and controlled the quarantine area, assessed raw material specification sampling and testing procedures. Tracked vendor quality metrics.

Quality Engineer (1988)

- Provided technical input for clinical and other studies.
- Assessed and approved deviations to manufacturing processes

Exhibit B

EXHIBIT B
Documents Reviewed

Expert Reports

1. Expert Report of Stephen S. Hecht, Ph.D., dated July 6, 2021.
2. Supplemental Expert Report of Stephen S. Hecht, Ph.D., dated October 31, 2022.
3. Expert Report of Ron Najafi, Ph.D., dated October 31, 2022.

ZHP Documents

1. ZHP02298856, the FDA's 483 for the July 23, 2018, to July 28, 2018, and July 30, 2018, to August 3, 2018 Inspection.
2. PRINSTON00162349, the FDA's EIR for the July 23, 2018, to July 28, 2018, and July 30, 2018, to August 3, 2018 Inspection.
3. PRINSTON00162407, the FDA's Letter Enclosing the EIR for the July 23, 2018, to July 28, 2018, and July 30, 2018, to August 3, 2018 Inspection.
4. ZHP00079956, the FDA's DMF Information Request, dated August 22, 2018.
5. ZHP00373843, August 26, 2018 Letter from Jun Du to the FDA Responding to the July 23 - August 3, 2018 Inspection.
6. ZHP00372959, Response to Observation 1 from the July 23 - August 3, 2018 Inspection.
7. ZHP00373072, Response to Observation 2 from the July 23 - August 3, 2018 Inspection.
8. ZHP00373146, Response to Observation 3 from the July 23 - August 3, 2018 Inspection.
9. ZHP00373246, Response to Observation 4 from the July 23 - August 3, 2018 Inspection.
10. ZHP00373263, Response to Observation 5 from the July 23 - August 3, 2018 Inspection.
11. ZHP00373294, Response to Observation 6 from the July 23 - August 3, 2018 Inspection.
12. ZHP00373376, Response to Observation 7 from the July 23 - August 3, 2018 Inspection.
13. ZHP00373487, Response to Observation 8 from the July 23 - August 3, 2018 Inspection.
14. ZHP00373492, Response to Observation 9 from the July 23 - August 3, 2018 Inspection.
15. ZHP00373782, Response to Observation 10 from the July 23 - August 3, 2018 Inspection.
16. ZHP00373801, Response to Observation 11 from the July 23 - August 3, 2018 Inspection.
17. PRINSTON00012473, September 2, 2018 Letter from Xiaodi Guo to the FDA Responding to Information Request Letter.
18. ZHP00079913, Response to DMF Information Request Letter.
19. ZHP00061068, September 21, 2018 Letter from the FDA to Jun Du.
20. PRINSTON00077339, the FDA's November 29, 2018 Warning Letter.
21. PRINSTON00074177, December 26, 2018 Letter from Jun Du to the FDA Enclosing ZHP's Response to the FDA's Warning Letter.
22. PRINSTON00282150, ZHP's Response to the FDA's Warning Letter.
23. PRINSTON00074174, the FDA's February 6, 2019 Letter to Jun Du Regarding ZHP's Response to the Warning Letter.

24. ZHP02224962, April 15, 2019 Email from Jun Du to the FDA Enclosing Additional Information Regarding the Warning Letter.
25. PRINSTON00158423, April 14, 2019 Letter from Jun Du to the FDA Enclosing Additional Information Regarding the Warning Letter.
26. PRINSTON00157232, the FDA's 483 for the May 20, 2019 to May 31, 2019 Inspection.
27. ZHP01447094, the FDA's EIR for the May 20, 2019 to May 31, 2019 Inspection.
28. PRINSTON00112003, ZHP's Response to the May 20 to 31, 2019 Inspection.
29. PRINSTON00081782, the FDA's EIR for the June 24 to 28, 2019 Inspection.
30. ZHP01429887, the FDA's EIR for the June 24 to 28, 2019 Inspection.
31. ZHP02420571, ZHP's Response to the June 24 to 28, 2019 Inspection.
32. PRINSTON00147028, September 4, 2019 Letter from the FDA to ZHP.
33. ZHP00397222, ZHP's Response to the September 4, 2019 Letter.
34. ZHP02561497, October 8, 2019 Email from Linda Lin to the FDA.
35. ZHP02561602, November 7, 2019 PowerPoint from ZHP.
36. ZHP02561504, ZHP's Response to Question 1 from the FDA.
37. ZHP02561534, ZHP's Response to Question 2 from the FDA.
38. ZHP02561543, ZHP's Response to Question 3 from the FDA.
39. ZHP02561551, Ad-Hoc Review Report of Quality System at Xunqiao API Site
40. ZHP02561600, ZHP's Response to Question 6 from the FDA.
41. ZHP00397961, December 2, 2019 Email from Linda Lin to the FDA.
42. ZHP00397973, ZHP Action Items, dated December 2, 2019.
43. ZHP02736683, the FDA's EIR for the July 19 to 29, 2021 Inspection.
44. ZHP02748797, October 26, 2021 Email from Linda Lin to the FDA.
45. ZHP02748800, ZHP's Petition for Expedited Removal from Detention without Physical Examination under Import Alert 66-40.
46. The FDA's Closeout Letter Regarding the November 29, 2018 Warning Letter.
47. ZHP02736709, November 10, 2021 Letter from the FDA to ZHP.
48. Stipulation of ZHP, including Exhibit 1.
49. ZHP01495187, Investigation of the Source of This Impurity
50. ZHP00243853, March 12, 2020 General Advice Letter from the FDA to ZHP Regarding N-Nitrosamines
51. ZHP01591089, Email Chain Enclosing March 1, 2019 General Advice Letter from the FDA to ZHP Regarding N-Nitrosamines
52. ZHP00116661, March 1, 2019 General Advice Letter from the FDA to ZHP Regarding N-Nitrosamines
53. ZHP02592303, February 13, 2019 Letter from Torrent's Vice-President (Legal) and Company Secretary to ZHP
54. PRINSTON00368120, March 22 – 28, 2014 Audit Report from Prinston to ZHP (ZHP 95)
55. PRINBURY00058078, Prinston's ANDA for Valsartan Tablets, USP, Characterisation of Impurities

56. PRINBURY00058083, Prinston's ANDA for Valsartan Tablets, USP, Justification of Specifications
57. PRINSTON00037968, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Dug Substance-Valsartan
58. PRINSTON00080011, ZHP's DMF for Valsartan, USP (Process II), Version US-02, Impurities
59. PRINSTON00177677, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Justification of Specifications
60. PRINSTON00183155, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Characterisation of Impurities
61. HUAHAI-US00007752, ZHP's DMF for Valsartan, USP (Process II), Version US-02.1, Impurities
62. ZHP01451842, Prinston's ANDA for Valsartan Tablets, USP, Dug Substance-Valsartan
63. PRINSTON00019870, Prinston's ANDA for Valsartan Tablets, USP, Manufacturing Process and Process Controls
64. PRINSTON00031790, November 19, 2015 Letter from Prinston to the FDA Regarding a CBE-0 Labeling Supplement
65. PRINSTON00033804, Prinston's ANDA for Valsartan Tablets, USP, Summary of Manufacturing Changes
66. PRINSTON00037376, August 22, 2014, Complete Response Letter from the FDA to Prinston Regarding ANDA for Valsartan Tablets, USP
67. PRINSTON00137623, Prinston's ANDA for Valsartan Tablets, USP, Summary of the CMC Response
68. PRINSTON00191105, June 20, 2013 Letter from Prinston to the FDA Regarding Bioequivalence Response to Information Request
69. PRINSTON00202890, July 2, 2013 Patent Amendment Letter from Prinston to the FDA
70. PRINSTON00233874, Prinston's ANDA for Valsartan Tablets, USP, Summary of Manufacturing Changes, June 09, 2015 – June 05, 2016
71. PRINSTON00272654, Prinston's ANDA for Valsartan Tablets, USP, Summary of Manufacturing Changes, June 09, 2017 – June 08, 2018
72. PRINSTON00284190, November 18, 2014 Resubmission/After Action Letter from Prinston to ZHP
73. SOLCO00025625, June 9, 2015 Approval Letter from the FDA to Prinston
74. PRINSTON00038063, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Pharmaceutical Development
75. PRINSTON00038151, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Batch Formula
76. PRINSTON00038158, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Controls of Critical Steps
77. PRINSTON00039378, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Specifications

78. PRINSTON00039383, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Analytic Procedures
79. PRINSTON00039858, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Batch Analysis
80. PRINSTON00054677August 7, 2014 Amendment Letter from Prinston to the FDA
81. PRINSTON00177304, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Manufacturing Process and Process Controls
82. PRINSTON00177447, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Analytical Procedures
83. PRINSTON00195424, June 12, 2014 Gratuitous BE Amendment Letter from Prinston to the FDA
84. PRINSTON00198218, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Manufacturing Process and Process Controls
85. PRINSTON00210760, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Drug Product
86. PRINSTON00211549, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Description and Composition of the Drug Product
87. PRINSTON00276130, Master Production Batch Record Approval for Valsartan and Hydrochlorothiazide Tablets
88. PRINSTON00276560, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Summary of the CBE-30 Supplement
89. PRINSTON00276575, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Analytic Procedures for API
90. PRINSTON00276579, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Analytical Procedures for API
91. SOLCO00025619, February 8, 2016 Approval Letter from the FDA to Prinston
92. ZHP00101881, June 2, 2015 Information Request Letter from Prinston to the FDA
93. ZHP00101882, Prinston's ANDA for Valsartan and Hydrochlorothiazide Tablets, USP, Response to BE Information Request, Summary of the Amendment
94. ZHP00101913, the FDA's Information Request #2 for ANDA 206083
95. PRINSTON00078386, ZHP's DMF for Valsartan, Table of Contents
96. PRINSTON00078403, ZHP's DMF for Valsartan, Manufacture
97. PRINSTON00078566, ZHP's DMF for Valsartan, Provess validation and / or evaluation
98. PRINSTON00077973, ZHP's Valsartan Batch Records
99. PRINSTON00078059, ZHP's DMF for Valsartan, Methods validation package
100. PRINSTON00078281, ZHP's DMF for Valsartan, Validation of the HS-GC Method For residual solvents in Valsartan
101. PRINSTON00078056, ZHP's DMF for Valsartan, Regional Information
102. PRINSTON00078361, ZHP's DMF for Valsartan, Validation for determination the residual tin in Valsartan by AAS method

103. PRINSTON00078379, ZHP's DMF for Valsartan, Validation for determination PSD in Valsartan by light diffraction method
104. PRINSTON00077836, ZHP's DMF for Valsartan, Appendices
105. PRINSTON00078571, ZHP's DMF for Valsartan, Characterisation
106. PRINSTON00078618, ZHP's DMF for Valsartan, Impurities
107. PRINSTON00078094, ZHP's DMF for Valsartan, Validation Of The HPLC Method For Valsartan related substances
108. PRINSTON00077888, ZHP's DMF for Valsartan, Master Batch Record Translation
109. PRINSTON00078700, ZHP's DMF for Valsartan, Control of drug substance
110. PRINSTON00078792, ZHP's DMF for Valsartan, Stability
111. PRINSTON00078749, ZHP's DMF for Valsartan, Container closure system
112. PRINSTON00078720, ZHP's DMF for Valsartan, Batch analysis
113. PRINSTON00078247, ZHP's DMF for Valsartan, Validation Of The HPLC Method For Valsartan Assay
114. PRINSTON00078732, ZHP's DMF for Valsartan, Reference standards or materials
115. PRINSTON00078714, ZHP's DMF for Valsartan, Validation of analytical procedures
116. PRINSTON00078548, ZHP's DMF for Valsartan, Control of critical steps and intermediates
117. PRINSTON00077830, February 14, 2017 Letter Closing ZHP's DMF 20939
118. PRINSTON00072137, ZHP's DMF for Valsartan, USP (Process II), Reference Standards or Materials
119. PRINSTON00071518, April 16, 2012 Amendment to ZHP's DMF for Valsartan, USP (Process II)
120. PRINSTON00072110, ZHP's DMF for Valsartan, USP (Process II), Validation of Analytical Procedures
121. PRINSTON00072117, ZHP's DMF for Valsartan, USP (Process II), Batch Analysis
122. PRINSTON00073076, ZHP's DMF for Valsartan, USP (Process II), Stability
123. PRINSTON00072213, March 1, 2013 DMF Annual Report
124. PRINSTON00072800, ZHP's DMF for Valsartan, USP (Process II), Impurities
125. PRINSTON00073053, ZHP's DMF for Valsartan, USP (Process II), Batch Analysis
126. PRINSTON00073120, December 10, 2013 Technical Amendment to ZHP's DMF 23491
127. PRINSTON00072610, ZHP's DMF for Valsartan, USP (Process II),Control of Materials
128. PRINSTON00072367, ZHP's DMF for Valsartan, USP (Process II), Master Batch Record of Drug Substance
129. PRINSTON00072582, ZHP's DMF for Valsartan, USP (Process II), Description of Manufacturing Process and Process Controls
130. PRINSTON00072235, ZHP's DMF for Valsartan, USP (Process II), Description of Process and Process Controls
131. PRINSTON00072267, ZHP's DMF for Valsartan, USP (Process II), Stability Data

132. PRINSTON00072260, ZHP's DMF for Valsartan, USP (Process II), Analytical Procedures
133. PRINSTON00072231, DMF Annual Report for Valsartan, USP (Process II)
134. PRINSTON00072285, DMF Annual Report for Valsartan, USP (Process II)
135. PRINSTON00072229, February 3, 2015 Annual Report, Amendment-005 for for Valsartan, USP (Process II)
136. PRINSTON00072338, ZHP's DMF for Valsartan, USP (Process II), Batch Analysis
137. PRINSTON00072307, ZHP's DMF for Valsartan, USP (Process II), Manufacture
138. PRINSTON00072310, ZHP's DMF for Valsartan, USP (Process II), Description of Manufacturing Process and Process Controls
139. PRINSTON00072302, DMF Annual Report for Valsartan USP (Process II)
140. ZHP00090262, DMF Annual Report for Valsartan USP (Process II)
141. ZHP00090441, March 3, 2017 Annual Report, Amendment-007 for Valsartan USP (Process II)
142. ZHP01460832, May 4, 2017 Amendment-008 for Valsartan USP (Process II)
143. PRINSTON00010626, February 14, 2018 Annual Report for Valsartan USP (Process II)
144. PRINSTON00000001-46, Prinston's June 18, 2018 Field Report to the FDA
145. ZHP00092392, Annual Report for Feb., 2018 through March., 2019
146. PRINSTON00269004, Valsartan USP
147. PRINSTON00141349, Valsartan and Hydrochlorothiazide Tablets USP
148. ZHP02614594, Valsartan Tablets USP
149. ZHP01303141, Valsartan USP
150. ZHP01916408, Valsartan USP
151. Certified Translation of ZHP00063836, Summary of Valsartan (Process II) Changes
152. Certified Translation of ZHP00063834, Change Request Form Attachment 2
153. Certified Translation of ZHP00063833, Change Request Form Attachment 1
154. Certified Translation of ZHP00063829, Change Request Form
155. Certified Translation of ZHP00063789, Change Control Form
156. PRINSTON00079747, April 16, 2012 Amendment to DMF for Valsartan, USP (Process II)
157. PRINSTON00071532, April 16, 2012 Annual Report from ZHP to the FDA Regarding Valsartan, USP (Process II)
158. ZHP01495186, July 1, 2018 Email Enclosing Investigation of the Source of this Impurity
159. ZHP02364173, NDMA and NDEA test results for all batches of Valsartan in USDMF grade
160. ZHP00671809, SOP TE-001-1
161. ZHP00400220, Email Chain Between ZHP and Novartis Regarding NDMA
162. ZHP00400281, Solvia's Report Identifying NDMA in ZHP's Valsartan
163. ZHP00400236, Novartis's Valsartan Testing Monograph

164. ZHP02214602-ZHP02214671, Novartis Documents
165. ZHP00671846, SMP-017 Deviation Investigation Management System
166. PRINSTON00249807, QS-F083 USP Valsartan and Hydrochlorothiazide Tablets USP Quality Standard
167. PRINSTON00235762, QS-A004 Valsartan USP Quality Standard
168. PRINSTON00221287, QS-A004 Valsartan USP Quality Standard
169. ZHP00114376, Prinston's SOP for Field Alert Reports
170. ZHP00114370, Prinston's SOP for External Audits
171. PRINBURY00040935, QS-F083 USP Valsartan and Hydrochlorothiazide Tablets USP Quality Standard
172. HUAHAI-US00010173, Site Master File for APIs
173. ZHP01447235, API-R&D-002 Guideline for Genotoxic impurity evaluation
174. ZHP02409670, SMP-021 Lab OOS/OOT Investigation Management System
175. ZHP02098970, SMP-017 Deviation Investigation Management System
176. ZHP01897709, SMP-021 Lab OOS/OOT Investigation Management System
177. ZHP01595770, SMP-013.05 Product Recall Management System
178. ZHP01492506, SMP-018 Change Control System
179. ZHP00703030, SMP-023 Quality Risk Management
180. ZHP00671846, SMP-017 Deviation Investigation Management System
181. ZHP00336196, SMP-011 Complaint management procedure
182. ZHP00247036, SMP-018 Change Control System
183. ZHP00005233, SMP-011 Complaint management procedure
184. ZHP00005067, SMP-021 Lab OOS/OOT Investigation Management System
185. ZHP00002272, SMP-013.05 Product Recall Management System
186. ZHP00002260, SMP-011 Complaint management procedure
187. ZHP00002234, SMP-020 Annual Product Review Management System
188. ZHP00000696, SMP-017 Deviation Investigation Management System
189. ZHP00000417, SMP-023 Quality Risk Management
190. ZHP00000369, SMP-018 Change Control System
191. HUAHAI-US00015719, SMP-021 Lab OOS/OOT Investigation Management System
192. Certified Translation of ZHP00000171
193. ZHP02633528-ZHP02633538
194. ZHP00405024-ZHP00405068
195. ZHP00380568-ZHP00380591
196. ZHP01748896-ZHP01748899-ZHP1748899 (ZHP 260)
197. ZHP00405069-ZHP00405070 (ZHP 277)
198. ZHP01320376-ZHP01320392 (ZHP 280)
199. ZHP00405021-ZHP00405023 (ZHP 284)
200. ZHP00359796-ZHP00359822 (ZHP 288)
201. ZHP02135008-ZHP02135025 (ZHP 289)
202. ZHP02173090-ZHP00371269 (ZHP 290)

Teva Documents

1. TEVA-MDL2875-00324735, September 13, 2018 Letter from Teva's Corporate Legal Department to ZHP
2. TEVA-MDL2875-00614800, April 15, 2019 Letter from Teva's General Counsel Corporate Affairs and Company Secretary
3. TEVA-MDL2875-00964314, October 19, 2018 Letter from ZHP to Teva's General Counsel Corporate Affairs and Company Secretary
4. TEVA-MDL2875-00762496, Valsartan USP
5. TEVA-MDL2875-00020214, Amendment to Quality Agreement between Watson and ZHP (TEVA 169)
6. TEVA-MDL2875-00020212, Quality Agreement between Arrow Pharm and ZHP (TEVA 170)
7. TEVA-MDL2875-00020213, Technical Agreement between Actavis and ZHP (TEVA 168)
8. TEVA-MDL2875-00020279, Quality Agreement between Actavis and ZHP (TEVA 167)
9. TEVA 230

Torrent Documents

1. TORRENT-MDL2875-00536415, July 5, 2013 Technical and Quality Agreement of Active Pharmaceutical Ingredients between Torrent and ZHP
2. TORRENT-MDL2875-00291332, May 7, 2017 Technical and Quality Agreement of Active Pharmaceutical Ingredients between Torrent and ZHP
3. TORRENT-MDL2875-00116577, Amlodipine, Valsartan and Hydrochlorothiazide Tablets USP
4. TORRENT-MDL2875-00232735, USP

Hetero Documents

1. HLL0119374, Valsartan USP

Regulatory Documents

1. Food and Drug Administration, Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry (Feb. 2021).
2. Food and Drug Administration, Guidance for Industry: Changes to an Approved NDA or ANDA (Apr. 2004)
3. Food and Drug Administration, Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (Dec. 2008)
4. USP's General Notices and Requirements

Deposition Testimony

1. David Chesney Deposition Transcript for March 21, 2022, with all exhibits:

- Ex. 1 Notice to Take Videotaped Deposition
- Ex. 2 ZHP Defendants' Response and Objections to Notice to Take Videotaped Oral Deposition of David Chesney
- Ex. 3 DL Chesney Consulting, LLC Invoices
- Ex. 4 Expert Report of David L. Chesney, MSJ
- Ex. 5 IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, May 1978
- Ex. 6 Document titled Purification of Laboratory Chemicals
- Ex. 7 Article in Tetrahedron, N,N-Dimethylformamide: Much more than a solvent
- Ex. 8 Sun, et al, Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine
- Ex. 9 PowerPoint titled Advanced analytical Technology Center (CEmat) Introduction
- Ex. 10 E-mail titled Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan, Bates ZHP00190573 and 574
- Ex. 11 PowerPoint titled Quality Management Essentials, Expert Advice on Building a Compliant System
- Ex. 12 Deviation Report Form, Bates ZHP00004352 through 4471
- Ex. 13 November 29, 2018 Warning Letter, Bates ZHP01344159 through 4164
- Ex. 14 Investigation Report, Bates ZHP00662283 through 2309
- Ex. 15 August 26, 2018 Response to FDA Inspection on July 23 - August 3, 3 2018, Bates ZHP02115600 through 5603..... 338
- Ex. 16 Establishment Inspection Report, Bates PRINSTON00162349 through 6 2406
- Defendant Ex. 1 January 25, 2019 FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues
- Defendant Ex. 2 August 30, 2018 FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

2. Eric Gu Deposition Transcripts for April 5-6, 2021, with all exhibits:

- ZHP 223 Notice of Deposition
- ZHP 224 Curriculum Vitae
- ZHP 225 PowerPoint Shanghai SynCores Technologies, Inc. July of 2013 ZHP-01397317
- ZHP 226 E-mail Thread 7 3/7/14 Subject, SynCores Presentation ZHP-01397314-15
- ZHP 227 Contract Assessment Table ZHP-00000215

- ZHP 228 Letter Re: Object: Submission of CAPA Plan to Joint Inspection ZHP 00493875-04
- ZHP 229 ICH Pharmaceutical Development Q8(R2) August 2009
- ZHP 230 ICH Quality Risk Management Q9 November 2005
- ZHP 231 Pharmaceutical Quality System Q10 June 2008
- ZHP 232 Final GMP Inspection Report ZHP 01862672-31
- ZHP 233 Study Report of Unknown Peak in Residual Solvent of Valsartan ZHP-01870977-19
- ZHP 234 E-mail Thread 2/11/19 Subject, PPT SYNCORES00032556-57
- ZHP 235 PowerPoint Project Review for Valsartan 2/9/19
- ZHP 236 Valsartan Quality Management Report ZHP00661535-90
- ZHP 42 Response to DMF 387 Information Request Letter
- ZHP 201 ICH Impurities in New Drug Substances Q3A(R2)
- ZHP 207 EMA, Questions And Answers on the Guideline on the Limits Of Genotoxic Impurities
- ZHP 213 Warning Letter 11/29/18 320-19-04 ZHP01344159-64
- ZHP 228 Letter Re: Object: Submission of CAPA Plan to Joint Inspection ZHP 00493875-04

3. Hai Wang Deposition Transcripts for March 10-11, 2021, with all exhibits:

- ZHP-42 Response to DMF Information Request Letter, Bates ZHP00079913 through 79945
- ZHP-107 First Amended Notice to Take Videotaped Oral Deposition
- ZHP-108 Mr. Wang's LinkedIn Profile
- ZHP-109 Excerpt from Prinston website
- ZHP-110 Excerpt from Prinston website
- ZHP-111 Excerpt from Prinston website, Welcome to Solco Healthcare
- ZHP-112 FDA-Approved Patient Labeling, Valsartan and Hydrochlorothiazide Tablets, USP, Bates PRINSTON00069311 and 312
- ZHP-113 November 10, 2016 document, Bates SOLCO00025875 and 25876
- ZHP-114 Spreadsheet, Bates SOLCO00028357
- ZHP-115 E-mail chain, Bates PRINSTON00102169 and 2170
- ZHP-116 Spreadsheet, Bates PRINSTON00102171
- ZHP-117 Spreadsheet, Bates PRINSTON00102172
- ZHP-118 Spreadsheet, SOLCO00028261
- ZHP-119 E-mail chain, Bates SOLCO00023690 through 3692
- ZHP-120 Spreadsheet, Bates SOLCO00023693
- ZHP-121 August 27, 2018 Letter, Bates PRINSTON00249966 through 9970

- ZHP-122 Quality Agreement dated as of January 2016 By and Between Prinston and ZHP
- ZHP-123 E-mail chain, Bates ZHP00097638 and 97639
- ZHP-124 E-mail chain, Bates PRINSTON00304062 through 4068
- ZHP-125 Letter titled Dear Recalling Firm, Bates PRINSTON00304082 through 304104
- ZHP-126 Spreadsheet, Bates PRINSTON00304108
- ZHP-127 7/13/18 e-mail, Bates SOLCO00024223
- ZHP-128 Document dated July 13, 2018, Bates SOLCO00024231 through 24235
- ZHP-129 Press Release, Bates SOCO00024226 through 24230
- ZHP-130 Valsartan and Valsartan HCTZ Products Return Response Form, Bates SOLCO00024224 and 24225
- ZHP-131 E-mail chain, Bates ZHP00084878 through 84881
- ZHP-132 E-mail chain, Bates PRINSTON00304052 through 4053
- ZHP-133 Spreadsheet, Bates SOLCO00027898
- ZHP-134 E-mail chain, Bates ZHP00084864 and 84865
- ZHP-135 E-mail chain, Bates ZHP00084727 and 84728
- ZHP-136 August 20, 2018 memo, Bates ZHP00084730 through 84736
- ZHP-137 E-mail chain, Bates SOLCO00142346 through 2348
- ZHP-138 February 22, 2019 letter, Bates PRINSTON00303144
- ZHP-139 E-mail chain, Bates ZHP00076107 through 76109
- ZHP-140 E-mail chain with attachment, Bates SOLCO00140700 through 720
- ZHP-141 Master Distribution Services Agreement, Bates SOLCO00184871 through 4887
- ZHP-142 Document titled Company Overview, Bates SOLCO000185712 through 5729
- ZHP 95 April 28, 2014 letter, with attachment, Bates PRINSTON00368120 through 8124
- ZHP-143 Spreadsheet, Bates SOLCO0004386
- ZHP-144 Master Distribution Services Agreement, Bates SOCOL000184917 through 184934
- ZHP-145 Spreadsheet, Bates SOLCO00034004
- ZHP-146 E-mail chain, Bates PRINSTON00097797 through 97801
- ZHP-147 E-mail chain, Bates ZHP01494578 and 4579
- ZHP-148 Press release, Bates ZHP01494580 through 4584
- ZHP-149 8/21/08 e-mail, Bates ZHP00084538
- ZHP-150 Press Release - Update on Valsartan API - a Statement from the Company, Bates ZHP00084539
- ZHP-151 May 16, 2018 Quotation Summary, Bates HUAHAI-US00000001

- ZHP-152 Recall analysis as of 2021-01-31.xlsx, Bates SOLCO000189643
- ZHP-153 January 4, 2017 e-mail, Bates SOLCO00034790
- ZHP-154 PowerPoint titled PrinJohnson, The Next Generation International Generic Pharmaceutical Company, JMP Healthcare Conference, January 11, 2017, Bates SOLCO00034791 through 34811
- ZHP-155 July 2017 Sales Performance Report, Bates PRINSTON00171721 through 1732
- ZHP-156 E-mail chain, Bates SOLCO00025367 and 25368
- ZHP-157 E-mail chain, Bates SOLCO000025179 through 25181
- ZHP-158 E-mail chain, Bates HUAHAI-US00001090 and 1091
- ZHP-159 Change Notification, Bates HUAHAI-US00001092 through 1102
- ZHP-160 E-mail chain, Bates ZHP00107730 through 7733
- ZHP-161 Change Notification, Bates ZHP00107734 and 7735

4. Jucai Ge Deposition Transcripts for April 27-30, 2021, with all exhibits:

- ZHP-322 CV
- ZHP-323 Job Description (JD-690-01) (English version); ZHP00000908 - 10
- ZHP-323A Job Description (JD-690-01) ZHP00000908 - 911
- ZHP-324 Standard Management Procedure, Title: Quality Manual; ZHP01793565 - 584
- ZHP-325 Standard Management Procedure, Title: Quality Manual (English version); ZHP02465424 - 447
- ZHP-326 Standard Management Procedure, Title: Corporate Documentation System
- ZHP-327 Standard Management Procedure, Title: Change Control System; ZHP00469139 – 162
- ZHP-328 Layout of Chuannan Site
- ZHP-329 Change Request Form
- ZHP-329A Change Request Form (English version)
- ZHP-330 Standard Management Procedure, Title: Deviation Investigation Management System; ZHP00410915 - 933
- ZHP-331 Deviation Investigation Report From; ZHP00000676 - 695
- ZHP-331A Deviation Investigation Report Form (English Translation); ZHP00165283 - 292
- ZHP-331B Investigation Report; ZHP01465846 – 858
- ZHP-295 E-mail dated 7/27/17; ZHP00190573 - 574
- ZHP-296 English translation of Exhibit ZHP-295
- ZHP-297 English version of Exhibit ZHP-298
- ZHP-298 Invention Patent Application; ZHP01812101 - 109

- ZHP-332 Quality Agreement Between Zhejiang Huahai Pharmaceutical Co., Ltd. & Shanghai SynCores Technologies, Inc.; ZHP00321576 - 579
- ZHP-332A English translation of Exhibit ZHP-332
- ZHP-333 Spreadsheet
- ZHP-333A Excel spreadsheet
- ZHP-333B Spreadsheet
- ZHP-213 Warning Letter from the US FDA, dated 11/29/2018 to Mr. Jun Du; ZHP01344159 - 164
- ZHP-334 copy of the annual product review management system; ZHP02671456 - 484
- ZHP-335 valsartan annual product quality review report; ZHP00065572 - 716
- ZHP-336 appendix to the 2015 annual product quality review report that is ZHP-335; ZHP00065621 - 716
- ZHP-337 Standard Management Procedure; ZHP00002260 - 271
- ZHP-338 US FDA Letter; ZHP01344159 - 164

5. Jun Du Deposition Transcripts for May 27-28, 2021, with all exhibits:

- ZHP-428 First Amended Notice of Deposition
- ZHP-429 Welcome to Prinbury Biopharm PRINBURY 00147760-86
- ZHP-430 Letter, 8/26/18 Response to FDA Inspection on July 23-August 3, 2018
- ZHP-431 CEMAT PowerPoint Chinese Version
- ZHP-432 CEMAT PowerPoint English Version
- ZHP-122 Quality Agreement 1/2016 Prinston and ZHP
- ZHP-127 E-mail Thread 7/13/18 Subject, Valsartan & Valsartan HCTZ Recall Notice And Press Release SOLCO 00024223 PRINSTON 00304110
- ZHP-128 Letter, 7/13/18 92 Re, Urgent Recall SOLCO 00024231-35
- ZHP-129 Prinston Pharma Issues Voluntary National Recall SOLCO 00024226-30
- ZHP-149 E-mail Thread 8/21/18 Subject, Press Release Valsartan Statement ZHP 0084538
- ZHP-150 Press Release Update on Valsartan API ZHP 00084539
- ZHP-210 Deviation Investigation Report PRINSTON 00075798-99
- ZHP-295 E-mail, 7/27/17 Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Chinese Version ZHP 00190573-74
- ZHP-296 E-mail, 7/27/17 Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities English Version ZHP 00190573-74
- ZHP-301 E-mail, 12/22/18 203 Subject, Summary of Reports with a Long Reporting Cycle Review Chinese Version ZHP 01391682

- ZHP-302 E-mail, 12/22/18 203 Subject, Summary of Reports with a Long Reporting Cycle Review English Version0
- ZHP-303 Project Name Description of Project Spreadsheets Chinese Version
- ZHP-304 Project Name Description of Project Spreadsheets English Version
- ZHP-305 Study Report of Unknown Peak in Residual Solvent Of Valsartan ZHP 01870977-19
- ZHP-433 Isolation and Identification Of Process Impurities (Jing Nie)
- ZHP-434 E-mail Thread 11/2/18 Subject, Happy Chinese New Year! ZHP 00675949-56
- ZHP-204 Deviation Report ZHP 00004352-71
- ZHP-212 Investigation Report 6/6/18 ZHP 00662283-09
- ZHP-213 Warning Letter 11/29/18 ZHP 01344159-64
- ZHP-312 Establishment Inspection Report 7/23/18 PRINSTON 00162349-06
- ZHP-319 E-mail Thread 7/17/18 Subject, Hello and Help CHARLESWANG 000447-49
- ZHP-321 Concise International Chemical Assessment Document 38 NDMA WHO 2002

6. Min Li Deposition Transcripts for April 20-22, 2021, with all exhibits:

- ZHP-208 Previously Marked. FDA Guidance for Industry, Draft Guidance
- ZHP-213 Previously Marked. 11/29/18 FDA Warning Letter, Bates ZHP01344159 through 4164
- ZHP-284 Previously Marked. E-mail chain, Bates ZHP00405021 through 5023
- ZHP-288 Previously Marked. E-mail with attachments, Bates ZHP00359796 through 9822
- ZHP-289 Previously Marked. Solvias report, Bates ZHP02135008 through 5025
- ZHP-291 Notice to Take Videotaped Deposition
- ZHP-292 Min Li, PhD's resume
- ZHP-293 Min Li's LinkedIn Profile
- ZHP-294 PowerPoint, Center for Excellence for Modern Analytical Technologies, Bates ZHP00404315 through 327
- ZHP-295 7/27/17 e-mail, Bates ZHP00190573 and 574
- ZHP-296 English translation of ZHP-295
- ZHP-297 Invention Patient Application, Bates ZHP01812101 through 2109
- ZHP-298 Chinese translation of ZHP-297
- ZHP-299 Valsartan Patent Investigation Report, Bates ZHP02336567 and ZHP02336682
- ZHP-300 Document titled SciFinder, Bates ZHP02336432 through 6434
- ZHP-301 12/22/18 e-mail, Bates ZHP01391682

- ZHP-302 English translation of ZHP-301
- ZHP-303 Excel spreadsheet, Summary of CEMAT reports
- ZHP-304 English version of ZHP-303
- ZHP-305 Study Report of Unknown Peak in Residual Solvent of Valsartan, Bates
- 22 ZHP01870977 through 1119
- ZHP-42 Previously marked. Response to DMF Information Request Letter, Bates ZHP00079913 through 9945
- ZHP-197 Previously marked. Article, N,N-Dimethylformamide: much more than a solvent
- ZHP-205 Previously marked. Document titled Valsartan, USP (Process II), Bates HUAHAI-US00007752 through 7923
- ZHP-206 Previously marked. Guideline on the Limits of Genotoxic Impurities
- ZHP-208 Previously Marked. Guidance for Industry, Genotoxic and Carcinogenic
- Impurities in Drug Substances and Products: Recommended Approaches
- ZHP-209 Previously marked. IARC Monographs
- ZHP-211 Previously marked. Sun, et al article, Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine, Bates ZHP01807298 through 7308
- ZHP-213 Previously marked. November 29, 2018 FDA Warning Letter, Bates ZHP01344159 through 4164
- ZHP-306 9/25/18 e-mail, Bates ZHP01390339
- ZHP-307 List of deficiency letters, Bates ZHP00457705 through 7707
- ZHP-308 Letter from FDA to Huahai US Inc., Bates PRINSTON00285416 through 5422
- ZHP-309 Wang, et al paper titled Development of Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry Methods for Analysis of DNA Adducts of Formaldehyde and Their Application to Rats Treated with N-Nitrosodimethylamine or 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, Bates ZHP00387118 through 7125
- ZHP-310 Draft Consensus Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities ini Pharmaceuticals to Limit Potential Carcinogenic Risk, M7
- ZHP-311 Textbook, Purification of Laboratory Chemicals
- ZHP-312 Establishment Inspection Report, Bates PRINSTON00162349 through 2406
- ZHP-313 E-mail chain, Bates ZHP00388607
- ZHP-314 Document titled Health effects of amines and derivatives associated with CO2 capture: Nitrosamines and nitramines
- ZHP-306-t English translation of ZHP-306
- ZHP-307-t English translation of ZHP-307

- ZHP-210 Previously marked. Deviation Investigation Report
- ZHP-212 Previously marked. Investigation regarding an unknown impurity, Bates ZHP00662283 through 2309
- ZHP-315 7/22/18 e-mail, Bates SYNCORES00028075
- ZHP-316 E-mail chain, Bates CHARLESWANG000239 through 291
- ZHP-317 Safety Data Sheet, Bates CHARLESWANG000310 through 317
- ZHP-318 6/22/18 e-mail, Bates CHARLESWANG000430
- ZHP-319 E-mail chain, Bates CHARLESWANG000447 through ZHP-320 Nonclinical Safety Assessment of N-nitrosodimethylamine (NMDA) and Recommended Limit in Drug Product, Bates CHARLESWANG000164 through 182
- ZHP-321 Concise International Chemical Assessment Document 38 regarding NDMA
- ZHP-315-t English translation of ZHP-315

7. Peng Dong Deposition Transcripts for March 29 to April 2, 2021, with all exhibits:

- ZHP-191 Notice to Take Videotaped Oral Deposition
- ZHP-192 Peng Dong's Curriculum Vitae
- ZHP-193 Guideline for Genotoxic Impurity Evaluation, Bates ZHP01447235 through 7242
- ZHP-194 Change Request Form, Chinese version, Bates ZHP00000161 through 214
- ZHP-195 Change Request Form, English6 version, Bates ZHP01843066 through 3119
- ZHP-196 Standard Management Procedure, Bates ZHP00469139 through 9162
- ZHP-197 Tetrahedron article, N,N-Dimethylformamide: Much more than a solvent
- ZHP-198 SC-1141 Valsartan Tetrazole New Process Project Report, Chinese version, Bates ZHP00000373 through 395
- ZHP-199 Research and development report of Valsartan, English version, Bates ZHP00076653 through 675
- ZHP-200 ICH guideline titled Impurities in New Drug Substances Q3A (R2)
- ZHP-201 English version of Exhibit ZHP-200, Impurities in New Drug Substances Q3A (R2)
- ZHP-202 December 10, 2013 letter to Drug Master File Staff, Subject DMF Amendment to Valsartan USP (Process II), DMF# 23491, Bates ZHP01713711
- ZHP-203 Amendment to Drug Master File, Valsartan USP (Process II), Bates PRINSTON00073102 through 73119
- ZHP-204 July 20, 2018 Deviation Investigation Report, Bates ZHP00004352 through 4471
- ZHP-205 Master Drug File amendment, Bates HUAHAI-US00007752 through 7923
- ZHP-206 Guideline on the Limits of Genotoxic Impurities

- ZHP-207 EMA Questions and answers on the "Guideline on the limits of genotoxic impurities"
- ZHP-208 Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches
- ZHP-209 IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans
- ZHP-210 Deviation Investigation Report, Bates PRINSTON00075797 through 76099
- ZHP-211 Sun, et al article, Theoretical Investigation of N-Nitrosodimethylamine
- formation from Nitrosation of Trimethylamine
- ZHP-212 Investigation Report, Bates ZHP00662283 through 2309
- ZHP-213 November 29, 2018 FDA Warning Letter, Bates ZHP01344159 through 4164
- ZHP-214 Final Process Validation Report, Bates ZHP00000227 through 372
- ZHP-215 SOP CC-1442, Bates ZHP01728787 through 8790
- ZHP-216 Deviation Investigation Report, Bates ZHP00668212 through 8239
- ZHP-217 Feasibility Study Report, Bates SYNCORES00037104 through 37191
- ZHP-218 Production Development Report, Bates ZHP01710580 through 647
- ZHP-219 Chinese version of Exhibit ZHP-218, Bates ZHP00063727 through 63772
- ZHP-220 Valsartan Impurities Profile Analysis Report, Bates ZHP00476862 through 6909
- ZHP-221 Chinese version of ZHP-220, Bates ZHP01613178 through 3223
- ZHP-222 SMP-018.07, Bates ZHP01420648 through 673

8. Michelle L. Osmian Deposition Transcript for May 6, 2021
9. Minli Zhang Deposition Transcripts for March 22-26, 2021, including all exhibits:

- ZHP-162 Minli Zhang's CV
- ZHP-163 Notice to Take Videotaped Oral Deposition
- ZHP-164 Presentation titled Welcome FDA Investigator Ms. Reba Gates & Ms. Kara Dobbin
- ZHP-165 SMP & SOP Management SMP & SOP List (Formulation), Bates PRINSTON00344354 through 344374
- ZHP-166 Site Master File, Bates ZHP02554975 through 2555026
- ZHP-167 Quality Agreement Dated as of March, 2017 By and Between Prinston Pharmaceutical, Inc. And Zhejiang Huahai Pharmaceutical Co. Ltd., Bates ZHP01890025 through 64
- ZHP-168 Standard Operation Procedure, Bates ZHP01596848 through 6900
- ZHP-169 Standard Management Procedure, Bates ZHP00000417 through 470
- ZHP-170 Pharmaceutical Analytical Development, Prinbury Biopharm Co., Ltd., Bates PRINBURY00040262 through 40266

- ZHP-171 July 19, 2016 e-mail, Bates PRINSTON00369875
- ZHP-172 Quality Agreement By and Between Zhejiang Huahai Pharmaceutical & Prinbury Biopharm, Bates PRINSTON00369897
- ZHP-173 Standard Management Procedure, Bates ZHP01492578 through 2623
- ZHP-174 E-mail chain with attachment, Bates PRINSTON00126870 through 6880
- ZHP-175 E-mail chain and attachment, Bates PRINSTON00227500 through 7506
- ZHP-176 SOP G-1005-2, Material Release Procedure, Bates ZHP01596774 through 6783
- ZHP-177 Method Validation Report, Bates Prinston00233497 through 3530
- ZHP-178 E-mail chain, Bates PRINSTON00127364 and 7365
- ZHP-179 E-mail chain with attachment, Bates ZHP00694865 through 4871
- ZHP-180 Certificate of Analysis, Bates ZHP00694872 through 4875
- ZHP-106 Change Notification, Bates ZHP00107734 and 7735
- ZHP-181 Attachment C - Change Request Notification and Approval Form, Bates ZHP00107751 through 7760
- ZHP-182 Quality Standard, Bates PRINSTON00221287 through 1295
- ZHP-183 Documents, Bates ZHP00206743 through 6751
- ZHP-184 E-mail chain with attachment, Bates PRINSTON00167120 through 7145
- ZHP-185 Investigation Report, Bates PRINSTON00319271 through 9276
- ZHP-186 Emergency Handling Notice of the Valsartan Impurity Incident, with attachments
- ZHP-187 Flowchart, Bates ZHP01578019
- ZHP-188 Research Protocol of NDMA for Valsartan API, Valsartan Tablets and Valsartan Hydrochlorothiazide Tablets, Bates ZHP02671638 through 1651
- ZHP-189 Excel spreadsheet, Bates ZHP02326538
- ZHP-190 The Special Self Inspection Report of FDF Factory, Bates PRINSTON00338455 through 8473
- ZHP-186A Chinese version of Exhibit ZHP-186

10. Remonda Gergis Deposition Transcript for February 2, 2021, including all exhibits:

- ZHP-88 Curriculum Vitae Remonda Gergis
- ZHP-89 E-mail Thread 17 1/27/10 Subject, Remonda PRINSTON00228656-59
- ZHP-90 Plaintiff's Translation of Exhibit
- ZHP-89 (No Bates)
- ZHP-91 Memo, 1/31/10 85 Subject, Bi-Weekly Highlights of Prinbury, Shanghai SOLCO00188847-50
- ZHP-92 Quality Agreement March 2017 Prinston and ZHP PRINSTON00345008-47
- ZHP-93 Audit Report 11/18-25/11 (No Bates)
- ZHP-94 Audit Report 4/18-25/13 (No Bates)

- ZHP-95 Audit Report 3/22-28/14 PRINSTON00368120-24
- ZHP-96 E-mail Thread 212 11/23/16 Subject, Notice of FDA Inspection 2016 PRINSTON00169379
- ZHP-97 To Whom It May Concern 11/21/16 PRINSTON00169380
- ZHP-98 FDA Inspection 7/11-13/16 PRINSTON00081547-48
- ZHP-99 FDA Inspection 11/14-18/16 PRINSTON00169538-41
- ZHP-100 E-mail Thread 9/8/15 Subject, Deviation Notification for Valsartan 80mg Tablets PRINSTON00170081-84
- ZHP-101 Deviation Investigation Report 8/2015 PRINSTON00170085-07
- ZHP-102 E-mail Thread 2/4/16 Subject, OOS-FQC15032 ZHP00114329-31
- ZHP-103 E-mail Thread 7/19/18 Subject, Teva Pharmaceuticals USA Issues Voluntary Nationwide Recall ZHP00108375-80
- ZHP-104 E-mail Thread 6/14/18 Subject, Potential FAR for Valsartan ZHP00110211
- ZHP-105 E-mail Thread 4/25/19 Subject, QA Refuses to Sign on Losartan Commitment Letter ZHP00090552-54
- ZHP-106 Change Notification 5/8/12 ZHP00107734-35

11. Qiangming Li Deposition Transcripts for April 13-16, 2021, including all exhibits:

- ZHP-255 Mr. Li's Curriculum Vitae
- ZHP-256 Standard Management Procedure, SMP-021.07, Bates ZHP00410888 through 914
- ZHP-257 E-mail chain, Bates ZHP00327507 and 7508
- ZHP-254A Notice to Take Videotaped Deposition
- ZHP-254B Chinese language version of Notice to Take Videotaped Deposition
- ZHP-260 E-mail chain, Bates ZHP01748896 through 8899
- ZHP-261 November 6, 2018 e-mail, Bates ZHP00404977 and 4978
- ZHP-262 Document titled Ranbaxy Laboratories Limited, Gurgaon, Analytical Research, Bates ZHP00405124 through 5127
- ZHP-263 Certificate of suitability, Bates ZHP01748900 through 8904
- ZHP-264 E-mail chain, Bates ZHP01748905 through 8913
- ZHP-265 E-mail chain, Bates ZHP02630924 and 925
- ZHP-266 Summary document, Bates ZHP02630926 and 927
- ZHP-267 E-mail chain, Bates ZHP00477534 through 7553
- ZHP-258A 1/16/19 e-mail, Bates ZHP02324735
- ZHP-258B Chinese version of ZHP-258A... 115
- ZHP-259A Final GMP Inspection report, Bates ZHP02324736 through 4795
- ZHP-259B Translated version of ZHP-259A
- ZHP-259C Translated version of ZHP-259A
- ZHP-260A Translated version of ZHP-260
- ZHP-261A Translated version of ZHP-261
- ZHP-263A Translated version of ZHP-263

- ZHP-264A Translated version of ZHP-264
- ZHP-264B Translated version of ZHP-264
- ZHP-265A Translation of ZHP-265
- ZHP-266A Translated version of Exhibit 266
- ZHP-267A Translated version of ZHP-267
- ZHP-267B Translated version of ZHP-267
- ZHP-268 E-mail chain, Bates ZHP02118072 through 8075
- ZHP-269 Attachment to Exhibit ZHP-268, Bates ZHP02118076 through 8095
- ZHP-270 E-mail chain, Bates ZHP00493010 through 3195
- ZHP-271 E-mail chain, Bates ZHP00496153 and 6154
- ZHP-272 Attachment to Exhibit ZHP-271, Summary of e-mail communications, Bates ZHP00496155 through 615
- ZHP-273 E-mail with attachment, Bates ZHP02118712 through 8731
- ZHP-274 E-mail chain, Bates ZHP02118423 through 8448
- ZHP-275 E-mail chain, Bates ZHP01318048 through 8075
- ZHP-276 Attachment to ZHP-276, justification process, Bates ZHP01318076 through 8078
- ZHP-277 November 17, 2016 e-mail, Bates ZHP00405069 and 5070
- ZHP-278 Chromatograms, Bates ZHP01313866 and 3867
- ZHP-279 E-mail chain, Bates ZHP01313602 through 3609
- ZHP-268A Translation of ZHP-268
- ZHP-270A Translation of ZHP-270
- ZHP-270B Translation of ZHP-270
- ZHP-272A Translation of Exhibit ZHP-272
- ZHP-273A Translation of Exhibit ZHP-273
- ZHP-274A Translation of Exhibit ZHP-274
- ZHP-274B Translation of Exhibit ZHP-274B
- ZHP-275A Translation of ZHP-275
- ZHP-276A Translation of ZHP-276
- ZHP-277A Translation of ZHP-277
- ZHP-277B Translation of ZHP-277
- ZHP-279A Translation of ZHP-279
- ZHP-280 E-mail chain, Bates ZHP01320376 through 392
- ZHP-281 E-mail chain, Bates ZHP02094739 through 4751
- ZHP-282 Investigation of Residual Solvents in Valsartan API and Impurities in Recovered Solvents, Bates ZHP00489560 through 9580
- ZHP-283 Novartis Testing Monograph, Bates ZHP00405024 through 5068
- ZHP-284 E-mail chain, Bates ZHP00405021 through 5023
- ZHP-285 E-mail chain, Bates ZHP02633528 through 3538
- ZHP-286 Study Report of Unknown Peak in Residual Solvent of Valsartan, Bates ZHP00389127 through 9269
- ZHP-287 Secondary Recordbook, Bates ZHP00405108 and 5109

- ZHP-288 E-mail chain, Bates ZHP00359796 through 5822
- ZHP-289 Solvias study, Valsartan: Identification of unknown compounds, Bates ZHP02135008 through 5025
- ZHP-290 Composite of chromatograms, Bates ZHP02173090 through 1269
- ZHP-280A Translated version of ZHP-280
- ZHP-281A Translation of ZHP-281
- ZHP-281B Translation of ZHP-281
- ZHP-281C Translated version of ZHP-281
- ZHP-282A Translation of ZHP-282
- ZHP-283A Translation of ZHP-283
- ZHP-284A Translation of ZHP-284
- ZHP-285A Translation of ZHP-285
- ZHP-288A Translation of ZHP-288
- ZHP-289A Translation of ZHP-289

12. John Iozzia Deposition Transcript for January 20, 2021, including all exhibits:

- ZHP-1 Notice of Videotaped Deposition
- ZHP-2 Curriculum Vitae John C. Iozzia
- ZHP-3 LinkedIn John C. Iozzia
- ZHP-4 Huahai Corporation Organization Chart HUAHAI-US00010966
- ZHP-5 Huahai US, Inc. Partner of Choice For APIs and Intermediates October 2013 (No Bates)
- ZHP-6 Welcome to Huahai 6/5/17 (No Bates)
- ZHP-7 Welcome to Zhejiang Huahai Pharmaceutical Co., Ltd. 6/13/17
- ZHP-8 E-mail Thread 4/19/17 Subject HUAHAI-US00006348
- ZHP-9 Zhejiang Huahai Pharmaceutical February 2017 (No Bates)
- ZHP-10 Site Master File For APIs HUAHAI-US00010173-37
- ZHP-11 Site Master File For API and Finished Dosage Forms HUAHAI-US00010238-11
- ZHP-12 API Sales Report 3/2012 HUAHAI-US00010001-09
- ZHP-13 E-mail Thread 3/8/12 Subject, Presentation HUAHAI-US00010000
- ZHP-14 E-mail Thread 5/17/12 Subject, Valsartan Change Notification HUAHAI-US00004164-68
- ZHP-15 Change Notification 5/8/12 HUAHAI-US00001092-02
- ZHP-16 E-mail Thread 1/29/13 Subject, Valsartan DMF #23491 HUAHAI-US00000511-12
- ZHP-17 E-mail Thread 9/23/14 Subject, Chromatograms For Related Compounds Test for Valsartan HUAHAI-US00007525-31
- ZHP-18 E-mail Thread 10/23/14 Subject, Chromatograms For Related Compounds HUAHAI-US00007581-90
- ZHP-19 Area Percent Report HUAHAI-US00007602-03

- ZHP-20 E-mail Thread 5/9/17 Subject, Please Respond ASAP HUAHAI-US00013105-09
- ZHP-21 E-mail Thread 11/8/17 Subject, Prinston Price List HUAHAI-US00014943-44
- ZHP-22 E-mail Thread 7/10/18 Subject, Huahai's ZHP00108371-72
- ZHP-23 E-mail Thread 7/2/18 Subject, Valsartan HUAHAI-US00006785-98
- ZHP-24 Active Pharmaceutical Ingredient (API) Supply Agreement HUAHAI-US00015212-31
- ZHP-25 E-mail Thread 7/19/18 Subject, Teva Pharmaceuticals USA ZHP00108375-80
- ZHP-26 E-mail Thread 7/25/18 Subject, Valsartan Recall in the USA HUAHAI-US00006877-78
- ZHP-27 Letter, 7/20/18 7/20/18 Subject, Valsartan API HUAHAI-US00006857
- ZHP-28 E-mail Thread 12 8/8/18 Subject, Valsartan Recall in the USA HUAHAI-US00006894-96
- ZHP-29 E-mail Thread 8/9/18 Subject, Valsartan Recall in the USA HUAHAI-US00009689-92
- ZHP-30 E-mail Thread 8/13/18 Subject, Valsartan Recall in the USA HUAHAI-US00006913-17
- ZHP-31 E-mail Thread 11/20/19 Subject, Valsartan Recall in the USA HUAHAI-US00007162-73
- ZHP-32 E-mail Thread 7/26/18 Subject, TOP Urgent!!! US FDA HUAHAI-US00015389
- ZHP-33 E-mail Thread 7/26/18 Subject, Urgent/FDA Info Request HUAHAI-US00006879-82
- ZHP-34 Certificate of Analysis HUAHAI-US00006883-86
- ZHP-35 E-mail Thread 2/27/15 Subject, DMF Open Part Request HUAHAI-US00007952-56
- ZHP-36 E-mail Thread 2/27/15 Subject, DM Open Part Request HUAHAI-US00007689-93
- ZHP-37 Potential Impurities In Valsartan HUAHAI-US00007752-23
- ZHP-38 E-mail Thread 10/17/19 Subject, GNTM-Corp-QRM 2019-037 Zhejiang Huahai HUAHAI-US00005408-11
- ZHP-39 E-mail Thread 10/23/19 Subject, GNTM-Corp-QRM 2019-037 Zhejiang Huahai HUAHAI-US00013831-39
- ZHP-40 E-mail Thread 1/16/20 Subject, Austar Pharma Claim Letter HUAHAI-US00013876-84
- ZHP-41 Response to CHMP List of Outstanding Issues ZHP02437848 ZHP02437867 ZHP02437872
- ZHP-42 Response to DMF Information Request Letter ZHP00079913-45
- ZHP-43 FDA Quality System ObservationsZHP00061069-79

13. Jucai Ge Deposition Transcripts for May 26-27, 2022, with all exhibits:

- ZHP-456A Second Amended Notice to Take Videotaped Oral Deposition
- ZHP-456B Chinese version of Second Amended Notice to Take Videotaped Oral
- Deposition
- ZHP-295 Previously marked. Chinese version of ZHP-296
- ZHP-296 Previously marked. Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan, Bates ZHP00190573 and 190574
- ZHP-431 Previously marked. Chinese version of PowerPoint
- ZHP-432 Previously marked. PowerPoint, Advanced analytical Technology Center (CEmat) Introduction
- ZHP-213A Previously marked. November 29, 2018 FDA warning letter
- ZHP-213B Previously marked. Chinese version of FDA warning letter
- ZHP-458A Binder of documents
- ZHP- 458B Chinese version of Binder of Documents
- ZHP-42 Previously marked. Response to DMF Information Request Letter, Bates
- 15 ZHP00079913 through 79945
- ZHP-170 Previously marked. Document Bates ZHP02336567 through 2336686
- ZHP-321 Previously marked. WHO document, Concise International Chemical Assessment Document 38
- ZHP-127A Previously marked. 7/13/18 e-mail with attachment, Bates SOLCO00024223 and PRINSTON00304110
- ZHP-127B Previously marked. Chinese version of ZHP-127A
- ZHP-128A Previously marked Recall notice
- ZHP-128B Previously marked Chinese version of 128A
- ZHP-460A Gomm et al Original Article, N-Nitrosodimethylamine- Contaminated Valsartan and the Risk of Cancer
- ZHP-460B Chinese version of Original Article
- ZHP-461A E-mail chain, Bates CHARLESWANG000271
- ZHP-461B Chinese version of ZHP-461A
- ZHP-462A 6/13/18 e-mail, Bates CHARLESWANG000318
- ZHP-462B Chinese version of ZHP-462A
- ZHP-463A 6-18-18 e-mail, Bates CHARLES WANG000391
- ZHP-463B Chinese version of 463A
- ZHP-464A June 21, 2018 e-mail, chain Bates CHARLESWANG000267
- ZHP-464B Chinese version of 464A
- ZHP-465A Document beginning To whom it may concern, Bates ZHP00374340 through 374356

- ZHP-465B Chinese version of 465A
- ZHP-466A Document Bates TEVA-MDL2875-00783229
- ZHP-466B Chinese version of 466A
- ZHP-467A E-mail chain, Bates TEVA-MDL00540386 through 540389
- ZHP-467B Chinese version of 467A
- ZHP-468A June 29, 2018 Toxicological Assessment for N-Nitrosodimethylamine (NDMA) in Valsartan Drug Substance, Bates TEVA-MDL2875-00068399
- ZHP-468B Chinese version of 468A
- ZHP-469A Invention Patent Application, ZHP01812101 through 1812109
- ZHP-469B Chinese version of 469A
- Defense 1A October 18, 2021 letter from US Food and Drug Administration with attached Establishment Inspection Report
- Defense 1B Chinese version of Defense 1A

Regulatory Documents

1. 21 CFR Part 210; Current Good Manufacturing Practices in Manufacturing, Processing, Packing or Holding of Drugs: General
2. 21 CFR Part 211; Current Good Manufacturing Practices for Finished Pharmaceuticals
3. 21 CFR 211.165(e) which states "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented."
4. 21 CFR 211.80 states that "[T]here shall be written procedures describing in sufficient detail the . . . testing . . . of [finished drug product] components…."
5. 21 CFR 211.84(d)(2) states that "[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals."
6. FDA Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)
7. FDA Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations
8. FDA Guidance for Industry – Process Validation: General Principles and Practices (2011)
9. FDA Guidance for Industry – Control of Nitrosamine Impurities in Human Drugs (2021)
10. EMA guidelines titled "Guideline on the Limits of Genotoxic Impurities" in effect from January 1, 2007 to January 31, 2018.
11. ICH Q3A Impurities in New Drug Substances
12. ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients
13. ICH Q8 titled: Pharmaceutical Development

14. ICH Q9 titled: Quality Risk Management
15. ICH Q10 titled: Pharmaceutical Quality System
16. ICH guideline titled, “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – M7,” dated February 6, 2013